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(57) Abstract

The invention provides 5 clones G52-24, H1075-1, J59-41, H83-22, J143-1 isolated from a human PBMC cDNA library and one clone M97-2 from a human glioblastoma cell line T98G cDNA library using a method of screening for cDNAs encoding secreted proteins. Determination of the nucleotide sequences and of the deduced amino acid sequences.

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SECRETED PROTEINS AND POLYNUCLEOTIDES ENCODING THEM

This application is a continuation-in-part of application Ser. No. 08/635,311, filed April 19, 1996.

FIELD OF THE INVENTION

The present invention provides novel polynucleotides and proteins encoded by such polynucleotides, along with therapeutic, diagnostic and research utilities for these polynucleotides and proteins.

BACKGROUND OF THE INVENTION

Technology aimed at the discovery of protein factors (including e.g., cytokines, such as lymphokines, interferons, CSFs and interleukins) has matured rapidly over the past decade. The now routine hybridization cloning and expression cloning techniques clone novel polynucleotides "directly" in the sense that they rely on information directly related to the discovered protein (i.e., partial DNA/amino acid sequence of the protein in the case of hybridization cloning; activity of the protein in the case of expression cloning). More recent "indirect" cloning techniques such as signal sequence cloning, which isolates DNA sequences based on the presence of a now well-recognized secretory leader sequence motif, as well as various PCR-based or low stringency hybridization cloning techniques, have advanced the state of the art by making available large numbers of DNA/amino acid sequences for proteins that are known to have biological activity by virtue of their secreted nature in the case of leader sequence cloning, or by virtue of the cell or tissue source in the case of PCR-based techniques. It is to these proteins and the polynucleotides encoding them that the present invention is directed.

SUMMARY OF THE INVENTION

In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:2;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:2 from nucleotide 1 to nucleotide 1014;

(c) a polynucleotide comprising the nucleotide sequence of the full length protein coding sequence of clone G52_24 deposited under accession number ATCC 98028;

(d) a polynucleotide encoding the full length protein encoded by the cDNA insert of clone G52_24 deposited under accession number ATCC 98028;

(e) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone G52_24 deposited under accession number ATCC 98028;

(f) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone G52_24 deposited under accession number ATCC 98028;

(g) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:3;

(h) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:3 having biological activity;

(i) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:26 from nucleotide 732 to nucleotide 1274;

(j) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:27;

(k) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(d) or (i) above;

(l) a polynucleotide which encodes a species homologue of the protein of (g), (h) or (j) above; and

(m) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(i).

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:2 from nucleotide 1 to nucleotide 1014; the nucleotide sequence of the full length protein coding sequence of clone G52_24 deposited under accession number ATCC 98028; or the nucleotide sequence of the mature protein coding sequence of clone G52_24 deposited under accession number ATCC 98028. In other preferred embodiments, the polynucleotide encodes the full length or mature protein encoded by the cDNA insert of clone G52_24 deposited under accession number ATCC 98028. In yet other preferred embodiments, the present invention provides a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:3 from amino acid 201 to amino acid 221.

Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:2, SEQ ID NO:1 or SEQ ID NO:4 .

In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:3;

(b) the amino acid sequence of SEQ ID NO:3 from amino acid 201 to amino acid 221;

(c) fragments of the amino acid sequence of SEQ ID NO:3; and

(d) the amino acid sequence encoded by the cDNA insert of clone G52_24 deposited under accession number ATCC98028;

(e) the amino acid sequence of SEQ ID NO:27;

(f) the amino acid sequence of SEQ ID NO:27 beginning with amino acid 41;

the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:3 or the amino acid sequence of SEQ ID NO:3 from amino acid 201 to amino acid 221.

In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:5;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:5 from nucleotide 181 to nucleotide 325;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:5 from nucleotide 274 to nucleotide 325;

(d) a polynucleotide comprising the nucleotide sequence of the full length protein coding sequence of clone M97_2 deposited under accession number ATCC 98028;

(e) a polynucleotide encoding the full length protein encoded by the cDNA insert of clone M97_2 deposited under accession number ATCC 98028;

(f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone M97_2 deposited under accession number ATCC 98028;

(g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone M97_2 deposited under accession number ATCC 98028;

(h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:6;

(i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:6 having biological activity;

(j) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:28 from nucleotide 171 to nucleotide 587;

(k) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:29;

(l) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) or (j) above; and

(m) a polynucleotide which encodes a species homologue of the protein of (h), (i) or (k) above .

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:5 from nucleotide 181 to nucleotide 325; the nucleotide sequence of SEQ ID NO:5 from nucleotide 274 to nucleotide 325; the nucleotide sequence of the full length protein coding sequence of clone M97_2 deposited under accession number ATCC 98028; or the nucleotide sequence of the mature protein coding sequence of clone M97_2 deposited under accession number ATCC 98028. In other preferred embodiments, the polynucleotide encodes the full length or mature protein encoded by the cDNA insert of clone M97_2 deposited under accession number ATCC 98028. In yet other preferred embodiments, the present invention provides a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:6 from amino acid 1 to amino acid 48.

Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:5, SEQ ID NO:7 or SEQ ID NO:28.

In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:6;

(b) the amino acid sequence of SEQ ID NO:6 from amino acid 1 to amino acid 48;

(c) fragments of the amino acid sequence of SEQ ID NO:6; and

(d) the amino acid sequence encoded by the cDNA insert of clone M97_2 deposited under accession number ATCC98028;

(e) the amino acid sequence of SEQ ID NO:29;

the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:6 or the amino acid sequence of SEQ ID NO:6 from amino acid 1 to amino acid 48.

In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:8;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:8 from nucleotide 36 to nucleotide 522;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:8 from nucleotide 93 to nucleotide 522;

(d) a polynucleotide comprising the nucleotide sequence of the full length protein coding sequence of clone H1075_1 deposited under accession number ATCC 98028;

(e) a polynucleotide encoding the full length protein encoded by the cDNA insert of clone H1075_1 deposited under accession number ATCC 98028;

(f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone H1075_1 deposited under accession number ATCC 98028;

(g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone H1075_1 deposited under accession number ATCC 98028;

(h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:9;

(i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:9 having biological activity;

(j) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:30 from nucleotide 19 to nucleotide 471;

(k) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:31;

(l) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) or (j) above; and

(m) a polynucleotide which encodes a species homologue of the protein of (h), (i) or (k) above.

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:8 from nucleotide 36 to nucleotide 522; the nucleotide sequence of SEQ ID NO:8 from nucleotide 93 to nucleotide 522; the nucleotide sequence of the full length protein coding sequence of clone H1075_1 deposited under accession number ATCC 98028; or the nucleotide sequence of the mature protein coding sequence of clone H1075_1 deposited under accession number ATCC 98028. In other preferred embodiments, the polynucleotide encodes the full length or mature protein encoded by the cDNA insert of clone H1075_1 deposited under accession number ATCC 98028. In yet other preferred embodiments, the present invention provides a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:9 from amino acid 1 to amino acid 101.

Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:8, SEQ ID NO:10 or SEQ ID NO:30.

In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:9;

(b) the amino acid sequence of SEQ ID NO:9 from amino acid 1 to amino acid 101;

(c) fragments of the amino acid sequence of SEQ ID NO:9;

(d) the amino acid sequence encoded by the cDNA insert of clone H1075_1 deposited under accession number ATCC98028;

(e) the amino acid sequence of SEQ ID NO:31; and

(f) the amino acid sequence of SEQ ID NO:31 beginning with amino acid 20;

the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:9 or the amino acid sequence of SEQ ID NO:9 from amino acid 1 to amino acid 101.

In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:11;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:11 from nucleotide 88 to nucleotide 499;

(c) a polynucleotide comprising the nucleotide sequence of the full length protein coding sequence of clone J59_41 deposited under accession number ATCC 98028;

(d) a polynucleotide encoding the full length protein encoded by the cDNA insert of clone J59_41 deposited under accession number ATCC 98028;

(e) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone J59_41 deposited under accession number ATCC 98028;

(f) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone J59_41 deposited under accession number ATCC 98028;

(g) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:12;

(h) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:12 having biological activity;

(i) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:32 from nucleotide 62 to nucleotide 1069;

(j) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:33 beginning with amino acid 185;

(k) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(f) or (i) above;

(l) a polynucleotide which encodes a species homologue of the protein of (g), (h) or (j) above; and

(m) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(i).

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:11 from nucleotide 88 to nucleotide 499; the nucleotide sequence of the full length protein coding sequence of clone J59_41 deposited under accession number ATCC 98028; or the nucleotide sequence of the mature protein coding sequence of clone J59_41 deposited under accession number ATCC 98028. In other preferred embodiments, the polynucleotide encodes the full length or mature protein encoded by the cDNA insert of clone J59_41 deposited under accession number ATCC 98028. In yet other preferred embodiments, the

present invention provides a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:12 from amino acid 45 to amino acid 113.

Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:11 or SEQ ID NO:13 or SEQ ID NO:32.

In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:12;

(b) the amino acid sequence of SEQ ID NO:12 from amino acid 45 to amino acid 113;

(c) fragments of the amino acid sequence of SEQ ID NO:12;

(d) the amino acid sequence encoded by the cDNA insert of clone J59_41 deposited under accession number ATCC98028;

(e) the amino acid sequence of SEQ ID NO:33;

(f) the amino acid sequence of SEQ ID NO:33 beginning with amion acid 185;

the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:12 or the amino acid sequence of SEQ ID NO:12 from amino acid 45 to amino acid 113.

In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:14;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:14 from nucleotide 138 to nucleotide 479;

(c) a polynucleotide comprising the nucleotide sequence of the full length protein coding sequence of clone H83_22 deposited under accession number ATCC 98028;

(d) a polynucleotide encoding the full length protein encoded by the cDNA insert of clone H83_22 deposited under accession number ATCC 98028;

(e) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone H83_22 deposited under accession number ATCC 98028;

(f) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone H83_22 deposited under accession number ATCC 98028;

(g) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:15;

(h) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:15 having biological activity;

(i) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:34 from nucleotide 56 to nucleotide 847;

(j) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:35;

(k) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(f) or (i) above;

(l) a polynucleotide which encodes a species homologue of the protein of (g), (h) or (j) above ; and

(m) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(j).

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:14 from nucleotide 138 to nucleotide 479; the nucleotide sequence of the full length protein coding sequence of clone H83_22 deposited under accession number ATCC 98028; or the nucleotide sequence of the mature protein coding sequence of clone H83_22 deposited under accession number ATCC 98028. In other preferred embodiments, the polynucleotide encodes the full length or mature protein encoded by the cDNA insert of clone H83_22 deposited under accession number ATCC 98028.

Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:14 or SEQ ID NO:16 or SEQ ID NO:34.

In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:15;

(b) fragments of the amino acid sequence of SEQ ID NO:15;

(c) the amino acid sequence encoded by the cDNA insert of clone H83_22 deposited under accession number ATCC98028; and

(d) the amino acid sequence of SEQ ID NO:35;

the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:15.

In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:17;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:17 from nucleotide 149 to nucleotide 461;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:17 from nucleotide 212 to nucleotide 461;

(d) a polynucleotide comprising the nucleotide sequence of the full length protein coding sequence of clone J143_1 deposited under accession number ATCC 98028;

(e) a polynucleotide encoding the full length protein encoded by the cDNA insert of clone J143_1 deposited under accession number ATCC 98028;

(f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone J143_1 deposited under accession number ATCC 98028;

(g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone J143_1 deposited under accession number ATCC 98028;

(h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:18;

(i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:18 having biological activity;

(j) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:36 from nucleotide 158 to nucleotide 910;

(k) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:37;

(l) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) or (j) above; and

(m) a polynucleotide which encodes a species homologue of the protein of (h), (i) or (k) above.

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:17 from nucleotide 149 to nucleotide 461; the nucleotide sequence of SEQ ID NO:17

from nucleotide 212 to nucleotide 461; the nucleotide sequence of the full length protein coding sequence of clone J143_1 deposited under accession number ATCC 98028; or the nucleotide sequence of the mature protein coding sequence of clone J143_1 deposited under accession number ATCC 98028. In other preferred embodiments, the polynucleotide encodes the full length or mature protein encoded by the cDNA insert of clone J143_1 deposited under accession number ATCC 98028.

Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:17 or SEQ ID NO:19 or SEQ ID NO:36.

In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:18;

(b) fragments of the amino acid sequence of SEQ ID NO:18;

(c) the amino acid sequence encoded by the cDNA insert of clone J143_1 deposited under accession number ATCC98028;

(d) the amino acid sequence of SEQ ID NO:36; and

(e) the amino acid sequence of SEQ ID NO:36 beginning with amino acid 22;

the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:18.

In certain preferred embodiments, the polynucleotide is operably linked to an expression control sequence. The invention also provides a host cell, including bacterial, yeast, insect and mammalian cells, transformed with such polynucleotide compositions.

Processes are also provided for producing a protein, which comprise:

(a) growing a culture of the host cell transformed with such polynucleotide compositions in a suitable culture medium; and

(b) purifying the protein from the culture.

The protein produced according to such methods is also provided by the present invention. Preferred embodiments include those in which the protein produced by such process is a mature form of the protein.

Protein compositions of the present invention may further comprise a pharmaceutically acceptable carrier. Compositions comprising an antibody which specifically reacts with such protein are also provided by the present invention.

Methods are also provided for preventing, treating or ameliorating a medical condition which comprises administering to a mammalian subject a therapeutically effective amount of a composition comprising a protein of the present invention and a pharmaceutically acceptable carrier.

BRIEF DESCRIPTION OF FIGURES

Fig. 1 is an autoradiograph evidencing the expression of the following clone(s) disclosed herein: G52_24.

Fig. 2 is an autoradiograph evidencing the expression of the following clone(s) disclosed herein: H83_22.

DETAILED DESCRIPTION

ISOLATED PROTEINS AND POLYNUCLEOTIDES

Nucleotide and amino acid sequences are reported below for each clone and protein disclosed in the present application. In some instances the sequences are preliminary and may include some incorrect or ambiguous bases or amino acids. The actual nucleotide sequence of each clone can readily be determined by sequencing of the deposited clone in accordance with known methods. The predicted amino acid sequence (both full length and mature) can then be determined from such nucleotide sequence. The amino acid sequence of the protein encoded by a particular clone can also be determined by expression of the clone in a suitable host cell, collecting the protein and determining its sequence.

For each disclosed protein applicants have identified what they have determined to be the reading frame best identifiable with sequence information available at the time of filing. Because of the partial ambiguity in reported sequence information, reported protein sequences include "Xaa" designators. These "Xaa" designators indicate either (1) a residue which cannot be identified because of nucleotide sequence ambiguity or (2) a stop codon in the determined nucleotide sequence where applicants believe one should not exist (if the nucleotide sequence were determined definitively).

As used herein a "secreted" protein is one which, when expressed in a suitable host cell, is transported across or through a membrane, including transport as a result of signal sequences in its amino acid sequence. "Secreted" proteins include without limitation proteins secreted wholly (e.g., soluble proteins) or partially (e.g. , receptors) from the cell in which they are expressed. "Secreted" proteins also include without limitation proteins which are transported across the membrane of the endoplpasmic reticulum.

Clone "G52_24"

A polynucleotide of the present invention has been identified as clone "G52_24". G52_24 was isolated from a human PBMC cDNA library using methods which are selective for cDNAs encoding secreted proteins. G52_24 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "G52_24 protein").

The nucleotide sequence of the 5' portion of G52_24 as presently determined is reported in SEQ ID NO:1. An additional internal nucleotide sequence from G52_24 as presently determined is reported in SEQ ID NO:2. What applicants believe is the proper reading frame and the predicted amino acid sequence encoded by such internal sequence is reported in SEQ ID NO:3. Additional nucleotide sequence from the 3' portion of G52_24, including the polyA tail, is reported in SEQ ID NO:4.

The nucleotide sequence disclosed herein for G52_24 was searched against the GenBank database using BLASTA/BLASTX and FASTA search protocols. G52_24 demonstrated at least some homology with the early activation cell surface antigen CD69 (GenPept accession number Z22576). The search also found hits at GenBank accession numbers R12300 and X87344. Based upon homology, G52_24 proteins and each homologous protein or peptide may share at least some activity.

Additional full-length nucleotide and amino acid sequence for G52_24 are provided in SEQ ID NO:26 and SEQ ID NO:27, respectively. Based on this sequence information applicants predict that the mature amino acid sequence for G52_24 begins with amino acid 41 of SEQ ID NO:27.

Clone "M97_2"

A polynucleotide of the present invention has been identified as clone "M97_2". M97_2 was isolated from a huam neural tissue (glioblastoma cell line T98G) cDNA library using methods which are selective for cDNAs encoding secreted proteins. M97_2 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "M97_2 protein").

The nucleotide sequence of the 5' portion of M97_2 as presently determined is reported in SEQ ID NO:5 What applicants presently believe is the proper reading frame for the coding region is indicated in SEQ ID NO:6. The predicted acid sequence of the M97_2 protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:6. Amino acids 1 to 31 are the predicted leader/signal sequence, with the predicted mature amino acid sequence beginning at amino acid 32. Additional nucleotide sequence from the 3' portion of M97_2, including the polyA tail, is reported in SEQ ID NO:7.

The nucleotide sequence disclosed herein for M97_2 was searched against the GenBank database using BLASTA/BLASTX and FASTA search protocols. M97_2 demonstrated at least some identity with an EST identified as "H. sapiens partial cDNA sequence; clone C6F07" (GenBank accession number Z25379). Based upon identity, M97_2 proteins and each identical protein or peptide may share at least some activity.

Additional full-length nucleotide and amino acid sequence for M97_2 are provided in SEQ ID NO:28 and SEQ ID NO:29, respectively.

Clone "H1075_1"

A polynucleotide of the present invention has been identified as clone "H1075_1". H1075_1 was isolated from a human PBMC cDNA library using methods which are selective for cDNAs encoding secreted proteins. H1075_1 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "H1075_1 protein").

The nucleotide sequence of the 5' portion of H1075_1 as presently determined is reported in SEQ ID NO:8 What applicants presently believe is the proper reading frame for the coding region is indicated in SEQ ID NO:9. The predicted acid sequence of the H1075_1 protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:9. Amino acids 1 to 19 are the predicted leader/signal sequence, with the predicted mature amino acid sequence beginning at amino acid 20. Additional nucleotide sequence from the 3' portion of H1075_1, including the polyA tail, is reported in SEQ ID NO:10.

The nucleotide sequence disclosed herein for H1075_1 was searched against the GenBank database using BLASTA/BLASTX and FASTA search protocols. H1075_1 demonstrated at least some identity with the sequence of a tissue specific secretory protein identified at GenBank accession number X67698 (GenPept A18921). Based upon identity, H1075_1 proteins and each identical protein or peptide may share at least some activity.

Additional full-length nucleotide and amino acid sequence for H1075_1 are provided in SEQ ID NO:30 and SEQ ID NO:31, respectively. Based on this sequence information applicants predict that the mature amino acid sequence for H1075_1 begins with amino acid 20 of SEQ ID NO:31.

Clone "J59_41"

A polynucleotide of the present invention has been identified as clone "J59_41". J59_41 was isolated from a human PBMC cDNA library using methods which are selective for cDNAs encoding secreted proteins. J59_41 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "J59_41 protein").

The nucleotide sequence of the 5' portion of J59_41 as presently determined is reported in SEQ ID NO:11 What applicants presently believe is the proper reading frame for the coding region is indicated in SEQ ID NO:12. The predicted acid sequence of the J59_41 protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:12. Additional nucleotide sequence from the 3' portion of J59_41, including the polyA tail, is reported in SEQ ID NO:13.

The nucleotide sequence disclosed herein for J59_41 was searched against the GenBank database using BLASTA/BLASTX and FASTA search protocols. J59_41 demonstrated at least some homology with the cosmid F54E7.1 gene product (caenorhabditis elegans). The search found a hit at GenBank accesion number R21739. Based upon homology, J59_41 proteins and each homologous protein or peptide may share at least some activity.

Additional full-length nucleotide and amino acid sequence for J59_41 are provided in SEQ ID NO:32 and SEQ ID NO:33, respectively. Based on this sequence information applicants predict that the mature amino acid sequence for J59_41 begins with amino acid 185 of SEQ ID NO:33.

Clone "H83_22"

A polynucleotide of the present invention has been identified as clone "H83_22". H83_22 was isolated from a human PBMC cDNA library using methods which are selective for cDNAs encoding secreted proteins. H83_22 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "H83_22 protein").

The nucleotide sequence of the 5' portion of H83_22 as presently determined is reported in SEQ ID NO:14 What applicants presently believe is the proper reading frame for the coding region is indicated in SEQ ID NO:15. The predicted acid sequence of the H83_22 protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:15. Additional nucleotide sequence from the 3' portion of H83_22, including the polyA tail, is reported in SEQ ID NO:16.

The nucleotide sequence disclosed herein for H83_22 was searched against the GenBank database using BLASTA/BLASTX and FASTA search protocols. No hits were found in the database. The amino acid sequence of H83_22 indicates that it may be a novel serine protease.

Additional full-length nucleotide and amino acid sequence for H83_22 are provided in SEQ ID NO:34 and SEQ ID NO:35, respectively.

Clone "J143_1"

A polynucleotide of the present invention has been identified as clone "J143_1". J143_1 was isolated from a human PBMC cDNA library using methods which are selective for cDNAs encoding secreted proteins. J143_1 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "J143_1 protein").

The nucleotide sequence of the 5' portion of J143_1 as presently determined is reported in SEQ ID NO:17 What applicants presently believe is the proper reading frame for the coding region is indicated in SEQ ID NO:18. The predicted acid sequence of the J143_1 protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:18. Amino acids 1 to 21 are the predicted leader/signal sequence, with the predicted mature amino acid sequence beginning at amino acid 22. Additional nucleotide sequence from the 3' portion of J143_1, including the polyA tail, is reported in SEQ ID NO:19.

The nucleotide sequence disclosed herein for J143_1 was searched against the GenBank database using BLASTA/BLASTX and FASTA search protocols. The clone showed at least some identity with an EST identified as "yh04a07.r1 H. sapiens cDNA clone 41951 5'".

Additional full-length nucleotide and amino acid sequence for J143_1 are provided in SEQ ID NO:36 and SEQ ID NO:37, respectively. Based on this sequence information applicants predict that the mature amino acid sequence for J143_1 begins with amino acid 22 of SEQ ID NO:37.

Figs. 1 and 2 are autoradiographs evidencing expression of clones of the present invention. All clones were expressed in COS cells.

Deposit of Clones

Clones G52_24, M97_2, H1075_1, J59_41, H83_22 and J143_1 were deposited on April 19, 1996 with the American Type Culture Collection under accession number ATCC 98028, from which each clone comprising a particular polynucleotide is obtainable. Each clone has been transfected into separate bacterial cells (*E. coli*) in this composite deposit. Bacterial cells containing a particular clone can be obtained from the composite deposit as follows:

An oligonucleotide probe or probes should be designed to the sequence that is known for that particular clone. This sequence can be derived from the sequences provided herein, or from a combination of those sequences. The sequence of the oligonucleotide

probe that was used to isolate each full-length clone is identified below, and should be most reliable in isolating the clone of interest.

Clone	Probe Sequence
G52_24	SEQ ID NO:20
M97_2	SEQ ID NO:21
H1075_1	SEQ ID NO:22
J59_41	SEQ ID NO:23
H83_22	SEQ ID NO:24
J143_1	SEQ ID NO:25

The design of the oligonucleotide probe should preferably follow these parameters:

(a) It should be designed to an area of the sequence which has the fewest ambiguous bases ("N's"), if any;

(b) It should be designed to have a T_m of approx. 80 ° C (assuming 2° for each A or T and 4 degrees for each G or C).

The oligonucleotide should preferably be labeled with g-^{32}P ATP (specific activity 6000 Ci/mmole) and T4 polynucleotide kinase using commonly employed techniques for labeling oligonucleotides. Other labeling techniques can also be used. Unincorporated label should preferably be removed by gel filtration chromatography or other established methods. The amount of radioactivity incorporated into the probe should be quantitated by measurement in a scintillation counter. Preferably, specific activity of the resulting probe should be approximately 4e+6 dpm/pmole.

The bacterial culture containing the pool of full-length clones should preferably be thawed and 100 μl of the stock used to inoculate a sterile culture flask containing 25 ml of sterile L-broth containing ampicillin at 100 μg/ml. The culture should preferably be grown to saturation at 37°C, and the saturated culture should preferably be diluted in fresh L-broth. Aliquots of these dilutions should preferably be plated to determine the dilution and volume which will yield approximately 5000 distinct and well-separated colonies on solid bacteriological media containing L-broth containing ampicillin at 100 μg/ml and agar at 1.5% in a 150 mm petri dish when grown overnight at 37°C. Other known methods of obtaining distinct, well-separated colonies can also be employed.

Standard colony hybridization procedures should then be used to transfer the colonies to nitrocellulose filters and lyse, denature and bake them.

The filter is then preferably incubated at 65°C for 1 hour with gentle agitation in 6X SSC (20X stock is 175.3 g NaCl/liter, 88.2 g Na citrate/liter, adjusted to pH 7.0 with NaOH) containing 0.5% SDS, 100 μg/ml of yeast RNA, and 10 mM EDTA (approximately 10 mL per 150 mm filter). Preferably, the probe is then added to the hybridization mix at a concentration greater than or equal to 1e+6 dpm/mL. The filter is then preferably incubated at 65°C with gentle agitation overnight. The filter is then preferably washed in 500 mL of 2X SSC/0.5% SDS at room temperature without agitation, preferably followed by 500 mL of 2X SSC/0.1% SDS at room temperature with gentle shaking for 15 minutes. A third wash with 0.1X SSC/0.5% SDS at 65°C for 30 minutes to 1 hour is optional. The filter is then preferably dried and subjected to autoradiography for sufficient time to visualize the positives on the X-ray film. Other known hybridization methods can also be employed.

The positive colonies are picked, grown in culture, and plasmid DNA isolated using standard procedures. The clones can then be verified by restriction analysis, hybridization analysis, or DNA sequencing.

Fragments of the proteins of the present invention which are capable of exhibiting biological activity are also encompassed by the present invention. Fragments of the protein may be in linear form or they may be cyclized using known methods, for example, as described in H.U. Saragovi, *et al.*, Bio/Technology 10, 773-778 (1992) and in R.S. McDowell, *et al.*, J. Amer. Chem. Soc. 114, 9245-9253 (1992), both of which are incorporated herein by reference. Such fragments may be fused to carrier molecules such as immunoglobulins for many purposes, including increasing the valency of protein binding sites. For example, fragments of the protein may be fused through "linker" sequences to the Fc portion of an immunoglobulin. For a bivalent form of the protein, such a fusion could be to the Fc portion of an IgG molecule. Other immunoglobulin isotypes may also be used to generate such fusions. For example, a protein - IgM fusion would generate a decavalent form of the protein of the invention.

The present invention also provides both full-length and mature forms of the disclosed proteins. The full-length form of the such proteins is identified in the sequence listing by translation of the nucleotide sequence of each disclosed clone. The mature form

of such protein may be obtained by expression of the disclosed full-length polynucleotide (preferably those deposited with ATCC) in a suitable mammalian cell or other host cell. The sequence of the mature form of the protein may also be determinable from the amino acid sequence of the full-length form.

The present invention also provides genes corresponding to the cDNA sequences disclosed herein. The corresponding genes can be isolated in accordance with known methods using the sequence information disclosed herein. Such methods include the preparation of probes or primers from the disclosed sequence information for identification and/or amplification of genes in appropriate genomic libraries or other sources of genomic materials.

Where the protein of the present invention is membrane-bound (e.g., is a receptor), the present invention also provides for soluble forms of such protein. In such forms part or all of the intracellular and transmembrane domains of the protein are deleted such that the protein is fully secreted from the cell in which it is expressed. The intracellular and transmembrane domains of proteins of the invention can be identified in accordance with known techniques for determination of such domains from sequence information.

Species homologs of the disclosed polynucleotides and proteins are also provided by the present invention. Species homologs may be isolated and identified by making suitable probes or primers from the sequences provided herein and screening a suitable nucleic acid source from the desired species.

The invention also encompasses allelic variants of the disclosed polynucleotides or proteins; that is, naturally-occurring alternative forms of the isolated polynucleotide which also encode proteins which are identical, homologous or related to that encoded by the polynucleotides .

The isolated polynucleotide of the invention may be operably linked to an expression control sequence such as the pMT2 or pED expression vectors disclosed in Kaufman *et al.*, Nucleic Acids Res. 19, 4485-4490 (1991), in order to produce the protein recombinantly. Many suitable expression control sequences are known in the art. General methods of expressing recombinant proteins are also known and are exemplified in R. Kaufman, Methods in Enzymology 185, 537-566 (1990). As defined herein "operably linked" means that the isolated polynucleotide of the invention and an expression control sequence are situated within a vector or cell in such a way that the protein is expressed by a host cell which has been transformed (transfected) with the ligated polynucleotide/expression control sequence.

A number of types of cells may act as suitable host cells for expression of the protein. Mammalian host cells include, for example, monkey COS cells, Chinese Hamster Ovary (CHO) cells, human kidney 293 cells, human epidermal A431 cells, human Colo205 cells, 3T3 cells, CV-1 cells, other transformed primate cell lines, normal diploid cells, cell strains derived from in vitro culture of primary tissue, primary explants, HeLa cells, mouse L cells, BHK, HL-60, U937, HaK or Jurkat cells.

Alternatively, it may be possible to produce the protein in lower eukaryotes such as yeast or in prokaryotes such as bacteria. Potentially suitable yeast strains include *Saccharomyces cerevisiae, Schizosaccharomyces pombe, Kluyveromyces* strains, *Candida,* or any yeast strain capable of expressing heterologous proteins. Potentially suitable bacterial strains include *Escherichia coli, Bacillus subtilis, Salmonella typhimurium,* or any bacterial strain capable of expressing heterologous proteins. If the protein is made in yeast or bacteria, it may be necessary to modify the protein produced therein, for example by phosphorylation or glycosylation of the appropriate sites, in order to obtain the functional protein. Such covalent attachments may be accomplished using known chemical or enzymatic methods.

The protein may also be produced by operably linking the isolated polynucleotide of the invention to suitable control sequences in one or more insect expression vectors, and employing an insect expression system. Materials and methods for baculovirus/insect cell expression systems are commercially available in kit form from, *e.g.*, Invitrogen, San Diego, California, U.S.A. (the MaxBac® kit), and such methods are well known in the art, as described in Summers and Smith, Texas Agricultural Experiment Station Bulletin No. 1555 (1987), incorporated herein by reference. As used herein, an insect cell capable of expressing a polynucleotide of the present invention is "transformed."

The protein of the invention may be prepared by culturing transformed host cells under culture conditions suitable to express the recombinant protein. The resulting expressed protein may then be purified from such culture (i.e., from culture medium or cell extracts) using known purification processes, such as gel filtration and ion exchange chromatography. The purification of the protein may also include an affinity column containing agents which will bind to the protein; one or more column steps over such affinity resins as concanavalin A-agarose, heparin-toyopearl® or Cibacrom blue 3GA Sepharose®; one or more steps involving hydrophobic interaction chromatography using such resins as phenyl ether, butyl ether, or propyl ether; or immunoaffinity chromatography.

Alternatively, the protein of the invention may also be expressed in a form which will facilitate purification. For example, it may be expressed as a fusion protein, such as those of maltose binding protein (MBP), glutathione-S-transferase (GST) or thioredoxin (TRX). Kits for expression and purification of such fusion proteins are commercially available from New England BioLab (Beverly, MA), Pharmacia (Piscataway, NJ) and InVitrogen, respectively. The protein can also be tagged with an epitope and subsequently purified by using a specific antibody directed to such epitope. One such epitope ("Flag") is commercially available from Kodak (New Haven, CT).

Finally, one or more reverse-phase high performance liquid chromatography (RP-HPLC) steps employing hydrophobic RP-HPLC media, e.g., silica gel having pendant methyl or other aliphatic groups, can be employed to further purify the protein. Some or all of the foregoing purification steps, in various combinations, can also be employed to provide a substantially homogeneous isolated recombinant protein. The protein thus purified is substantially free of other mammalian proteins and is defined in accordance with the present invention as an "isolated protein."

The protein of the invention may also be expressed as a product of transgenic animals, e.g., as a component of the milk of transgenic cows, goats, pigs, or sheep which are characterized by somatic or germ cells containing a nucleotide sequence encoding the protein.

The protein may also be produced by known conventional chemical synthesis. Methods for constructing the proteins of the present invention by synthetic means are known to those skilled in the art. The synthetically-constructed protein sequences, by virtue of sharing primary, secondary or tertiary structural and/or conformational characteristics with proteins may possess biological properties in common therewith, including protein activity. Thus, they may be employed as biologically active or immunological substitutes for natural, purified proteins in screening of therapeutic compounds and in immunological processes for the development of antibodies.

The proteins provided herein also include proteins characterized by amino acid sequences similar to those of purified proteins but into which modification are naturally provided or deliberately engineered. For example, modifications in the peptide or DNA sequences can be made by those skilled in the art using known techniques. Modifications of interest in the protein sequences may include the alteration, substitution, replacement, insertion or deletion of a selected amino acid residue in the coding sequence. For example, one or more of the cysteine residues may be deleted or replaced with another amino acid

to alter the conformation of the molecule. Techniques for such alteration, substitution, replacement, insertion or deletion are well known to those skilled in the art (see, e.g., U.S. Patent No. 4,518,584). Preferably, such alteration, substitution, replacement, insertion or deletion retains the desired activity of the protein.

Other fragments and derivatives of the sequences of proteins which would be expected to retain protein activity in whole or in part and may thus be useful for screening or other immunological methodologies may also be easily made by those skilled in the art given the disclosures herein. Such modifications are believed to be encompassed by the present invention.

USES AND BIOLOGICAL ACTIVITY

The polynucleotides and proteins of the present invention are expected to exhibit one or more of the uses or biological activities (including those associated with assays cited herein) identified below. Uses or activities described for proteins of the present invention may be provided by administration or use of such proteins or by administration or use of polynucleotides encoding such proteins (such as, for example, in gene therapies or vectors suitable for introduction of DNA).

Research Uses and Utilities

The polynucleotides provided by the present invention can be used by the research community for various purposes. The polynucleotides can be used to express recombinant protein for analysis, characterization or therapeutic use; as markers for tissues in which the corresponding protein is preferentially expressed (either constitutively or at a particular stage of tissue differentiation or development or in disease states); as molecular weight markers on Southern gels; as chromosome markers or tags (when labeled) to identify chromosomes or to map related gene positions; to compare with endogenous DNA sequences in patients to identify potential genetic disorders; as probes to hybridize and thus discover novel, related DNA sequences; as a source of information to derive PCR primers for genetic fingerprinting; as a probe to "subtract-out" known sequences in the process of discovering other novel polynucleotides; for selecting and making oligomers for attachment to a "gene chip" or other support, including for examination of expression patterns; to raise anti-protein antibodies using DNA immunization techniques; and as an antigen to raise anti-DNA antibodies or elicit another immune response. Where the polynucleotide encodes a protein which binds or potentially binds to another protein (such as, for example, in a

receptor-ligand interaction), the polynucleotide can also be used in interaction trap assays (such as, for example, that described in Gyuris et al., Cell 75:791-803 (1993)) to identify polynucleotides encoding the other protein with which binding occurs or to identify inhibitors of the binding interaction.

The proteins provided by the present invention can similarly be used in assay to determine biological activity, including in a panel of multiple proteins for high-throughput screening; to raise antibodies or to elicit another immune response; as a reagent (including the labeled reagent) in assays designed to quantitatively determine levels of the protein (or its receptor) in biological fluids; as markers for tissues in which the corresponding protein is preferentially expressed (either constitutively or at a particular stage of tissue differentiation or development or in a disease state); and, of course, to isolate correlative receptors or ligands. Where the protein binds or potentially binds to another protein (such as, for example, in a receptor-ligand interaction), the protein can be used to identify the other protein with which binding occurs or to identify inhibitors of the binding interaction. Proteins involved in these binding interactions can also be used to screen for peptide or small molecule inhibitors or agonists of the binding interaction.

Any or all of these research utilities are capable of being developed into reagent grade or kit format for commercialization as research products.

Methods for performing the uses listed above are well known to those skilled in the art. References disclosing such methods include without limitation "Molecular Cloning: A Laboratory Manual", 2d ed., Cold Spring Harbor Laboratory Press, Sambrook, J., E.F. Fritsch and T. Maniatis eds., 1989, and "Methods in Enzymology: Guide to Molecular Cloning Techniques", Academic Press, Berger, S.L. and A.R. Kimmel eds., 1987.

Nutritional Uses

Polynucleotides and proteins of the present invention can also be used as nutritional sources or supplements. Such uses include without limitation use as a protein or amino acid supplement, use as a carbon source, use as a nitrogen source and use as a source of carbohydrate. In such cases the protein or polynucleotide of the invention can be added to the feed of a particular organism or can be administered as a separate solid or liquid preparation, such as in the form of powder, pills, solutions, suspensions or capsules. In the case of microorganisms, the protein or polynucleotide of the invention can be added to the medium in or on which the microorganism is cultured.

Cytokine and Cell Proliferation/Differentiation Activity

A protein of the present invention may exhibit cytokine, cell proliferation (either inducing or inhibiting) or cell differentiation (either inducing or inhibiting) activity or may induce production of other cytokines in certain cell populations. Many protein factors discovered to date, including all known cytokines, have exhibited activity in one or more factor dependent cell proliferation assays, and hence the assays serve as a convenient confirmation of cytokine activity. The activity of a protein of the present invention is evidenced by any one of a number of routine factor dependent cell proliferation assays for cell lines including, without limitation, 32D, DA2, DA1G, T10, B9, B9/11, BaF3, MC9/G, M+ (preB M+), 2E8, RB5, DA1, 123, T1165, HT2, CTLL2, TF-1, Mo7e and CMK.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Assays for T-cell or thymocyte proliferation include without limitation those described in: Current Protocols in Immunology, Ed by J. E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 3, In Vitro assays for Mouse Lymphocyte Function 3.1-3.19; Chapter 7, Immunologic studies in Humans); Takai et al., J. Immunol. 137:3494-3500, 1986; Bertagnolli et al., J. Immunol. 145:1706-1712, 1990; Bertagnolli et al., Cellular Immunology 133:327-341, 1991; Bertagnolli, et al., J. Immunol. 149:3778-3783, 1992; Bowman et al., J. Immunol. 152: 1756-1761, 1994.

Assays for cytokine production and/or proliferation of spleen cells, lymph node cells or thymocytes include, without limitation, those described in: Polyclonal T cell stimulation, Kruisbeek, A.M. and Shevach, E.M. In *Current Protocols in Immunology*. J.E.e.a. Coligan eds. Vol 1 pp. 3.12.1-3.12.14, John Wiley and Sons, Toronto. 1994; and Measurement of mouse and human Interferon γ, Schreiber, R.D. In *Current Protocols in Immunology*. J.E.e.a. Coligan eds. Vol 1 pp. 6.8.1-6.8.8, John Wiley and Sons, Toronto. 1994.

Assays for proliferation and differentiation of hematopoietic and lymphopoietic cells include, without limitation, those described in: Measurement of Human and Murine Interleukin 2 and Interleukin 4, Bottomly, K., Davis, L.S. and Lipsky, P.E. In *Current Protocols in Immunology*. J.E.e.a. Coligan eds. Vol 1 pp. 6.3.1-6.3.12, John Wiley and Sons, Toronto. 1991; deVries et al., J. Exp. Med. 173:1205-1211, 1991; Moreau et al., Nature 336:690-692, 1988; Greenberger et al., Proc. Natl. Acad. Sci. U.S.A. 80:2931-2938, 1983; Measurement of mouse and human interleukin 6 - Nordan, R. In

Current Protocols in Immunology. J.E.e.a. Coligan eds. Vol 1 pp. 6.6.1-6.6.5, John Wiley and Sons, Toronto. 1991; Smith et al., Proc. Natl. Acad. Sci. U.S.A. 83:1857-1861, 1986; Measurement of human Interleukin 11 - Bennett, F., Giannotti, J., Clark, S.C. and Turner, K. J. In *Current Protocols in Immunology.* J.E.e.a. Coligan eds. Vol 1 pp. 6.15.1 John Wiley and Sons, Toronto. 1991; Measurement of mouse and human Interleukin 9 - Ciarletta, A., Giannotti, J., Clark, S.C. and Turner, K.J. In *Current Protocols in Immunology.* J.E.e.a. Coligan eds. Vol 1 pp. 6.13.1, John Wiley and Sons, Toronto. 1991.

Assays for T-cell clone responses to antigens (which will identify, among others, proteins that affect APC-T cell interactions as well as direct T-cell effects by measuring proliferation and cytokine production) include, without limitation, those described in: Current Protocols in Immunology, Ed by J. E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 3, In Vitro assays for Mouse Lymphocyte Function; Chapter 6, Cytokines and their cellular receptors; Chapter 7, Immunologic studies in Humans); Weinberger et al., Proc. Natl. Acad. Sci. USA 77:6091-6095, 1980; Weinberger et al., Eur. J. Immun. 11:405-411, 1981; Takai et al., J. Immunol. 137:3494-3500, 1986; Takai et al., J. Immunol. 140:508-512, 1988.

Immune Stimulating or Suppressing Activity

A protein of the present invention may also exhibit immune stimulating or immune suppressing activity, including without limitation the activities for which assays are described herein. A protein may be useful in the treatment of various immune deficiencies and disorders (including severe combined immunodeficiency (SCID)), e.g., in regulating (up or down) growth and proliferation of T and/or B lymphocytes, as well as effecting the cytolytic activity of NK cells and other cell populations. These immune deficiencies may be genetic or be caused by viral (e.g., HIV) as well as bacterial or fungal infections, or may result from autoimmune disorders. More specifically, infectious diseases causes by viral, bacterial, fungal or other infection may be treatable using a protein of the present invention, including infections by HIV, hepatitis viruses, herpesviruses, mycobacteria, Leishmania spp., malaria spp. and various fungal infections such as candidiasis. Of course, in this regard, a protein of the present invention may also be useful where a boost to the immune system generally may be desirable, *i.e.*, in the treatment of cancer.

Autoimmune disorders which may be treated using a protein of the present invention include, for example, connective tissue disease, multiple sclerosis, systemic lupus

erythematosus, rheumatoid arthritis, autoimmune pulmonary inflammation, Guillain-Barre syndrome, autoimmune thyroiditis, insulin dependent diabetes mellitis, myasthenia gravis, graft-versus-host disease and autoimmune inflammatory eye disease. Such a protein of the present invention may also to be useful in the treatment of allergic reactions and conditions, such as asthma (particularly allergic asthma) or other respiratory problems. Other conditions, in which immune suppression is desired (including, for example, organ transplantation), may also be treatable using a protein of the present invention.

Using the proteins of the invention it may also be possible to immune responses, in a number of ways. Down regulation may be in the form of inhibiting or blocking an immune response already in progress or may involve preventing the induction of an immune response. The functions of activated T cells may be inhibited by suppressing T cell responses or by inducing specific tolerance in T cells, or both. Immunosuppression of T cell responses is generally an active, non-antigen-specific, process which requires continuous exposure of the T cells to the suppressive agent. Tolerance, which involves inducing non-responsiveness or anergy in T cells, is distinguishable from immunosuppression in that it is generally antigen-specific and persists after exposure to the tolerizing agent has ceased. Operationally, tolerance can be demonstrated by the lack of a T cell response upon reexposure to specific antigen in the absence of the tolerizing agent.

Down regulating or preventing one or more antigen functions (including without limitation B lymphocyte antigen functions (such as , for example, B7)), *e.g.*, preventing high level lymphokine synthesis by activated T cells, will be useful in situations of tissue, skin and organ transplantation and in graft-versus-host disease (GVHD). For example, blockage of T cell function should result in reduced tissue destruction in tissue transplantation. Typically, in tissue transplants, rejection of the transplant is initiated through its recognition as foreign by T cells, followed by an immune reaction that destroys the transplant. The administration of a molecule which inhibits or blocks interaction of a B7 lymphocyte antigen with its natural ligand(s) on immune cells (such as a soluble, monomeric form of a peptide having B7-2 activity alone or in conjunction with a monomeric form of a peptide having an activity of another B lymphocyte antigen (*e.g.*, B7-1, B7-3) or blocking antibody), prior to transplantation can lead to the binding of the molecule to the natural ligand(s) on the immune cells without transmitting the corresponding costimulatory signal. Blocking B lymphocyte antigen function in this matter prevents cytokine synthesis by immune cells, such as T cells, and thus acts as an immunosuppressant Moreover, the lack of costimulation may also be sufficient to anergize the T cells, thereby

inducing tolerance in a subject. Induction of long-term tolerance by B lymphocyte antigen-blocking reagents may avoid the necessity of repeated administration of these blocking reagents. To achieve sufficient immunosuppression or tolerance in a subject, it may also be necessary to block the function of a combination of B lymphocyte antigens.

The efficacy of particular blocking reagents in preventing organ transplant rejection or GVHD can be assessed using animal models that are predictive of efficacy in humans. Examples of appropriate systems which can be used include allogeneic cardiac grafts in rats and xenogeneic pancreatic islet cell grafts in mice, both of which have been used to examine the immunosuppressive effects of CTLA4Ig fusion proteins *in vivo* as described in Lenschow *et al.*, Science *257*:789-792 (1992) and Turka *et al.*, Proc. Natl. Acad. Sci USA, *89*:11102-11105 (1992). In addition, murine models of GVHD (see Paul ed., Fundamental Immunology, Raven Press, New York, 1989, pp. 846-847) can be used to determine the effect of blocking B lymphocyte antigen function *in vivo* on the development of that disease.

Blocking antigen function may also be therapeutically useful for treating autoimmune diseases. Many autoimmune disorders are the result of inappropriate activation of T cells that are reactive against self tissue and which promote the production of cytokines and autoantibodies involved in the pathology of the diseases. Preventing the activation of autoreactive T cells may reduce or eliminate disease symptoms. Administration of reagents which block costimulation of T cells by disrupting receptor:ligand interactions of B lymphocyte antigens can be used to inhibit T cell activation and prevent production of autoantibodies or T cell-derived cytokines which may be involved in the disease process. Additionally, blocking reagents may induce antigen-specific tolerance of autoreactive T cells which could lead to long-term relief from the disease. The efficacy of blocking reagents in preventing or alleviating autoimmune disorders can be determined using a number of well-characterized animal models of human autoimmune diseases. Examples include murine experimental autoimmune encephalitis, systemic lupus erythmatosis in MRL/*lpr/lpr* mice or NZB hybrid mice, murine autoimmune collagen arthritis, diabetes mellitus in NOD mice and BB rats, and murine experimental myasthenia gravis (see Paul ed., Fundamental Immunology, Raven Press, New York, 1989, pp. 840-856).

Upregulation of an antigen function (preferably a B lymphocyte antigen function), as a means of up regulating immune responses, may also be useful in therapy. Upregulation of immune responses may be in the form of enhancing an existing immune response or eliciting an initial immune response. For example, enhancing an immune

response through stimulating B lymphocyte antigen function may be useful in cases of viral infection. In addition, systemic viral diseases such as influenza, the common cold, and encephalitis might be alleviated by the administration of stimulatory forms of B lymphocyte antigens systemically.

Alternatively, anti-viral immune responses may be enhanced in an infected patient by removing T cells from the patient, costimulating the T cells *in vitro* with viral antigen-pulsed APCs either expressing a peptide of the present invention or together with a stimulatory form of a soluble peptide of the present invention and reintroducing the *in vitro* activated T cells into the patient. Another method of enhancing anti-viral immune responses would be to isolate infected cells from a patient, transfect them with a nucleic acid encoding a protein of the present invention as described herein such that the cells express all or a portion of the protein on their surface, and reintroduce the transfected cells into the patient. The infected cells would now be capable of delivering a costimulatory signal to, and thereby activate, T cells *in vivo*.

In another application, up regulation or enhancement of antigen function (preferably B lymphocyte antigen function) may be useful in the induction of tumor immunity. Tumor cells (*e.g.*, sarcoma, melanoma, lymphoma, leukemia, neuroblastoma, carcinoma) transfected with a nucleic acid encoding at least one peptide of the present invention can be administered to a subject to overcome tumor-specific tolerance in the subject. If desired, the tumor cell can be transfected to express a combination of peptides . For example, tumor cells obtained from a patient can be transfected *ex vivo* with an expression vector directing the expression of a peptide having B7-2-like activity alone, or in conjunction with a peptide having B7-1-like activity and/or B7-3-like activity. The transfected tumor cells are returned to the patient to result in expression of the peptides on the surface of the transfected cell. Alternatively, gene therapy techniques can be used to target a tumor cell for transfection *in vivo*.

The presence of the peptide of the present invention having the activity of a B lymphocyte antigen(s) on the surface of the tumor cell provides the necessary costimulation signal to T cells to induce a T cell mediated immune response against the transfected tumor cells. In addition, tumor cells which lack MHC class I or MHC class II molecules, or which fail to reexpress sufficient amounts of MHC class I or MHC class II molecules, can be transfected with nucleic acid encoding all or a portion of (*e.g.*, a cytoplasmic-domain truncated portion) of an MHC class I α chain protein and β_2 microglobulin protein or an MHC class II α chain protein and an MHC class II β chain protein to thereby express MHC

class I or MHC class II proteins on the cell surface. Expression of the appropriate class I or class II MHC in conjunction with a peptide having the activity of a B lymphocyte antigen (*e.g.*,B7-1, B7-2, B7-3) induces a T cell mediated immune response against the transfected tumor cell. Optionally, a gene encoding an antisense construct which blocks expression of an MHC class II associated protein, such as the invariant chain, can also be cotransfected with a DNA encoding a peptide having the activity of a B lymphocyte antigen to promote presentation of tumor associated antigens and induce tumor specific immunity. Thus, the induction of a T cell mediated immune response in a human subject may be sufficient to overcome tumor-specific tolerance in the subject.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Suitable assays for thymocyte or splenocyte cytotoxicity include, without limitation, those described in: Current Protocols in Immunology, Ed by J. E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 3, In Vitro assays for Mouse Lymphocyte Function 3.1-3.19; Chapter 7, Immunologic studies in Humans); Herrmann et al., Proc. Natl. Acad. Sci. USA 78:2488-2492, 1981; Herrmann et al., J. Immunol. 128:1968-1974, 1982; Handa et al., J. Immunol. 135:1564-1572, 1985; Takai et al., J. Immunol. 137:3494-3500, 1986; Takai et al., J. Immunol. 140:508-512, 1988; Herrmann et al., Proc. Natl. Acad. Sci. USA 78:2488-2492, 1981; Herrmann et al., J. Immunol. 128:1968-1974, 1982; Handa et al., J. Immunol. 135:1564-1572, 1985; Takai et al., J. Immunol. 137:3494-3500, 1986; Bowmanet al., J. Virology 61:1992-1998; Takai et al., J. Immunol. 140:508-512, 1988; Bertagnolli et al., Cellular Immunology 133:327-341, 1991; Brown et al., J. Immunol. 153:3079-3092, 1994.

Assays for T-cell-dependent immunoglobulin responses and isotype switching (which will identify, among others, proteins that modulate T-cell dependent antibody responses and that affect Th1/Th2 profiles) include, without limitation, those described in: Maliszewski, J. Immunol. 144:3028-3033, 1990; and Assays for B cell function: *In vitro* antibody production, Mond, J.J. and Brunswick, M. In *Current Protocols in Immunology*. J.E.e.a. Coligan eds. Vol 1 pp. 3.8.1-3.8.16, John Wiley and Sons, Toronto. 1994.

Mixed lymphocyte reaction (MLR) assays (which will identify, among others, proteins that generate predominantly Th1 and CTL responses) include, without limitation, those described in: Current Protocols in Immunology, Ed by J. E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W Strober, Pub. Greene Publishing Associates

and Wiley-Interscience (Chapter 3, In Vitro assays for Mouse Lymphocyte Function 3.1-3.19; Chapter 7, Immunologic studies in Humans); Takai et al., J. Immunol. 137:3494-3500, 1986; Takai et al., J. Immunol. 140:508-512, 1988; Bertagnolli et al., J. Immunol. 149:3778-3783, 1992.

Dendritic cell-dependent assays (which will identify, among others, proteins expressed by dendritic cells that activate naive T-cells) include, without limitation, those described in: Guery et al., J. Immunol. 134:536-544, 1995; Inaba et al., Journal of Experimental Medicine 173:549-559, 1991; Macatonia et al., Journal of Immunology 154:5071-5079, 1995; Porgador et al., Journal of Experimental Medicine 182:255-260, 1995; Nair et al., Journal of Virology 67:4062-4069, 1993; Huang et al., Science 264:961-965, 1994; Macatonia et al., Journal of Experimental Medicine 169:1255-1264, 1989; Bhardwaj et al., Journal of Clinical Investigation 94:797-807, 1994; and Inaba et al., Journal of Experimental Medicine 172:631-640, 1990.

Assays for lymphocyte survival/apoptosis (which will identify, among others, proteins that prevent apoptosis after superantigen induction and proteins that regulate lymphocyte homeostasis) include, without limitation, those described in: Darzynkiewicz et al., Cytometry 13:795-808, 1992; Gorczyca et al., Leukemia 7:659-670, 1993; Gorczyca et al., Cancer Research 53:1945-1951, 1993; Itoh et al., Cell 66:233-243, 1991; Zacharchuk, Journal of Immunology 145:4037-4045, 1990; Zamai et al., Cytometry 14:891-897, 1993; Gorczyca et al., International Journal of Oncology 1:639-648, 1992.

Assays for proteins that influence early steps of T-cell commitment and development include, without limitation, those described in: Antica et al., Blood 84:111-117, 1994; Fine et al., Cellular Immunology 155:111-122, 1994; Galy et al., Blood 85:2770-2778, 1995; Toki et al., Proc. Nat. Acad Sci. USA 88:7548-7551, 1991.

Hematopoiesis Regulating Activity

A protein of the present invention may be useful in regulation of hematopoiesis and, consequently, in the treatment of myeloid or lymphoid cell deficiencies. Even marginal biological activity in support of colony forming cells or of factor-dependent cell lines indicates involvement in regulating hematopoiesis, e.g. in supporting the growth and proliferation of erythroid progenitor cells alone or in combination with other cytokines, thereby indicating utility, for example, in treating various anemias or for use in conjunction with irradiation/chemotherapy to stimulate the production of erythroid precursors and/or erythroid cells; in supporting the growth and proliferation of myeloid cells such as

granulocytes and monocytes/macrophages (i.e., traditional CSF activity) useful, for example, in conjunction with chemotherapy to prevent or treat consequent myelo-suppression; in supporting the growth and proliferation of megakaryocytes and consequently of platelets thereby allowing prevention or treatment of various platelet disorders such as thrombocytopenia, and generally for use in place of or complimentary to platelet transfusions; and/or in supporting the growth and proliferation of hematopoietic stem cells which are capable of maturing to any and all of the above-mentioned hematopoietic cells and therefore find therapeutic utility in various stem cell disorders (such as those usually treated with transplantation, including, without limitation, aplastic anemia and paroxysmal nocturnal hemoglobinuria), as well as in repopulating the stem cell compartment post irradiation/chemotherapy, either *in-vivo* or *ex-vivo* (i.e., in conjunction with bone marrow transplantation or with peripheral progenitor cell transplantation (homologous or heterologous)) as normal cells or genetically manipulated for gene therapy.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Suitable assays for proliferation and differentiation of various hematopoietic lines are cited above.

Assays for embryonic stem cell differentiation (which will identify, among others, proteins that influence embryonic differentiation hematopoiesis) include, without limitation, those described in: Johansson et al. Cellular Biology 15:141-151, 1995; Keller et al., Molecular and Cellular Biology 13:473-486, 1993; McClanahan et al., Blood 81:2903-2915, 1993.

Assays for stem cell survival and differentiation (which will identify, among others, proteins that regulate lympho-hematopoiesis) include, without limitation, those described in: Methylcellulose colony forming assays, Freshney, M.G. In *Culture of Hematopoietic Cells*. R.I. Freshney, *et al.* eds. Vol pp. 265-268, Wiley-Liss, Inc., New York, NY. 1994; Hirayama et al., Proc. Natl. Acad. Sci. USA 89:5907-5911, 1992; Primitive hematopoietic colony forming cells with high proliferative potential, McNiece, I.K. and Briddell, R.A. In *Culture of Hematopoietic Cells*. R.I. Freshney, *et al.* eds. Vol pp. 23-39, Wiley-Liss, Inc., New York, NY. 1994; Neben et al., Experimental Hematology 22:353-359, 1994; Cobblestone area forming cell assay, Ploemacher, R.E. In *Culture of Hematopoietic Cells*. R.I. Freshney, *et al.* eds. Vol pp. 1-21, Wiley-Liss, Inc.., New York, NY. 1994; Long term bone marrow cultures in the presence of stromal cells, Spooncer, E., Dexter, M. and Allen, T. In *Culture of Hematopoietic Cells*. R.I. Freshney, *et al.* eds. Vol pp. 163-179,

Wiley-Liss, Inc., New York, NY. 1994; Long term culture initiating cell assay, Sutherland, H.J. In *Culture of Hematopoietic Cells*. R.I. Freshney, *et al.* eds. Vol pp. 139-162, Wiley-Liss, Inc., New York, NY. 1994.

Tissue Growth Activity

A protein of the present invention also may have utility in compositions used for bone, cartilage, tendon, ligament and/or nerve tissue growth or regeneration, as well as for wound healing and tissue repair and replacement, and in the treatment of burns, incisions and ulcers.

A protein of the present invention, which induces cartilage and/or bone growth in circumstances where bone is not normally formed, has application in the healing of bone fractures and cartilage damage or defects in humans and other animals. Such a preparation employing a protein of the invention may have prophylactic use in closed as well as open fracture reduction and also in the improved fixation of artificial joints. *De novo* bone formation induced by an osteogenic agent contributes to the repair of congenital, trauma induced, or oncologic resection induced craniofacial defects, and also is useful in cosmetic plastic surgery.

A protein of this invention may also be used in the treatment of periodontal disease, and in other tooth repair processes. Such agents may provide an environment to attract bone-forming cells, stimulate growth of bone-forming cells or induce differentiation of progenitors of bone-forming cells. A protein of the invention may also be useful in the treatment of osteoporosis or osteoarthritis, such as through stimulation of bone and/or cartilage repair or by blocking inflammation or processes of tissue destruction (collagenase activity, osteoclast activity, etc.) mediated by inflammatory processes.

Another category of tissue regeneration activity that may be attributable to the protein of the present invention is tendon/ligament formation. A protein of the present invention, which induces tendon/ligament-like tissue or other tissue formation in circumstances where such tissue is not normally formed, has application in the healing of tendon or ligament tears, deformities and other tendon or ligament defects in humans and other animals. Such a preparation employing a tendon/ligament-liketissue inducing protein may have prophylactic use in preventing damage to tendon or ligament tissue, as well as use in the improved fixation of tendon or ligament to bone or other tissues, and in repairing defects to tendon or ligament tissue. De novo tendon/ligament-liketissue formation induced by a composition of the present invention contributes to the repair of congenital, trauma

induced, or other tendon or ligament defects of other origin, and is also useful in cosmetic plastic surgery for attachment or repair of tendons or ligaments. The compositions of the present invention may provide an environment to attract tendon- or ligament-forming cells, stimulate growth of tendon- or ligament-forming cells, induce differentiation of progenitors of tendon- or ligament-forming cells, or induce growth of tendon/ligament cells or progenitors *ex vivo* for return *in vivo* to effect tissue repair. The compositions of the invention may also be useful in the treatment of tendinitis, carpal tunnel syndrome and other tendon or ligament defects. The compositions may also include an appropriate matrix and/or sequestering agent as a carrier as is well known in the art.

The protein of the present invention may also be useful for proliferation of neural cells and for regeneration of nerve and brain tissue, *i.e.* for the treatment of central and peripheral nervous system diseases and neuropathies, as well as mechanical and traumatic disorders, which involve degeneration, death or trauma to neural cells or nerve tissue. More specifically, a protein may be used in the treatment of diseases of the peripheral nervous system, such as peripheral nerve injuries, peripheral neuropathy and localized neuropathies, and central nervous system diseases, such as Alzheimer's, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, and Shy-Drager syndrome. Further conditions which may be treated in accordance with the present invention include mechanical and traumatic disorders, such as spinal cord disorders, head trauma and cerebrovascular diseases such as stroke. Peripheral neuropathies resulting from chemotherapy or other medical therapies may also be treatable using a protein of the invention.

Proteins of the invention may also be useful to promote better or faster closure of non-healing wounds, including without limitation pressure ulcers, ulcers associated with vascular insufficiency, surgical and traumatic wounds, and the like.

It is expected that a protein of the present invention may also exhibit activity for generation or regeneration of other tissues, such as organs (including, for example, pancreas, liver, intestine, kidney, skin, endothelium), muscle (smooth, skeletal or cardiac) and vascular (including vascular endothelium) tissue, or for promoting the growth of cells comprising such tissues. Part of the desired effects may be by inhibition or modulation of fibrotic scarring to allow normal tissue to regenerate. A protein of the invention may also exhibit angiogenic activity.

A protein of the present invention may also be useful for gut protection or regeneration and treatment of lung or liver fibrosis, reperfusion injury in various tissues, and conditions resulting from systemic cytokine damage.

A protein of the present invention may also be useful for promoting or inhibiting differentiation of tissues described above from precursor tissues or cells; or for inhibiting the growth of tissues described above.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Assays for tissue generation activity include, without limitation, those described in: International Patent Publication No. WO95/16035 (bone, cartilage, tendon); International Patent Publication No. WO95/05846 (nerve, neuronal); International Patent Publication No. WO91/07491 (skin, endothelium).

Assays for wound healing activity include, without limitation, those described in: Winter, Epidermal Wound Healing, pps. 71-112 (Maibach, HI and Rovee, DT, eds.), Year Book Medical Publishers, Inc., Chicago, as modified by Eaglstein and Mertz, J. Invest. Dermatol 71:382-84 (1978).

Activin/Inhibin Activity

A protein of the present invention may also exhibit activin- or inhibin-related activities. Inhibins are characterized by their ability to inhibit the release of follicle stimulating hormone (FSH), while activins and are characterized by their ability to stimulate the release of follicle stimulating hormone (FSH). Thus, a protein of the present invention, alone or in heterodimers with a member of the inhibin α family, may be useful as a contraceptive based on the ability of inhibins to decrease fertility in female mammals and decrease spermatogenesis in male mammals. Administration of sufficient amounts of other inhibins can induce infertility in these mammals. Alternatively, the protein of the invention, as a homodimer or as a heterodimer with other protein subunits of the inhibin-β group, may be useful as a fertility inducing therapeutic, based upon the ability of activin molecules in stimulating FSH release from cells of the anterior pituitary. See, for example, United States Patent 4,798,885. A protein of the invention may also be useful for advancement of the onset of fertility in sexually immature mammals, so as to increase the lifetime reproductive performance of domestic animals such as cows, sheep and pigs.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Assays for activin/inhibin activity include, without limitation, those described in: Vale et al., Endocrinology 91:562-572, 1972; Ling et al., Nature 321:779-782, 1986; Vale et al., Nature 321:776-779, 1986; Mason et al., Nature 318:659-663, 1985; Forage et al., Proc. Natl. Acad. Sci. USA 83:3091-3095, 1986.

Chemotactic/Chemokinetic Activity

A protein of the present invention may have chemotactic or chemokinetic activity (e.g., act as a chemokine) for mammalian cells, including, for example, monocytes, fibroblasts, neutrophils, T-cells, mast cells, eosinophils, epithelial and/or endothelial cells. Chemotactic and chemokinetic proteins can be used to mobilize or attract a desired cell population to a desired site of action. Chemotactic or chemokinetic proteins provide particular advantages in treatment of wounds and other trauma to tissues, as well as in treatment of localized infections. For example, attraction of lymphocytes, monocytes or neutrophils to tumors or sites of infection may result in improved immune responses against the tumor or infecting agent.

A protein or peptide has chemotactic activity for a particular cell population if it can stimulate, directly or indirectly, the directed orientation or movement of such cell population. Preferably, the protein or peptide has the ability to directly stimulate directed movement of cells. Whether a particular protein has chemotactic activity for a population of cells can be readily determined by employing such protein or peptide in any known assay for cell chemotaxis.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Assays for chemotactic activity (which will identify proteins that induce or prevent chemotaxis) consist of assays that measure the ability of a protein to induce the migration of cells across a membrane as well as the ability of a protein to induce the adhesion of one cell population to another cell population. Suitable assays for movement and adhesion include, without limitation, those described in: Current Protocols in Immunology, Ed by J.E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W.Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 6.12, Measurement of alpha and beta Chemokines 6.12.1-6.12.28; Taub et al. J. Clin. Invest. 95:1370-1376, 1995; Lind et al. APMIS 103:140-146, 1995; Muller et al Eur. J. Immunol. 25: 1744-1748; Gruber et al. J. of Immunol. 152:5860-5867, 1994; Johnston et al. J. of Immunol. 153: 1762-1768, 1994.

Hemostatic and Thrombolytic Activity

A protein of the invention may also exhibit hemostatic or thrombolytic activity. As a result, such a protein is expected to be useful in treatment of various coagulation disorders (including hereditary disorders, such as hemophilias) or to enhance coagulation and other hemostatic events in treating wounds resulting from trauma, surgery or other causes. A protein of the invention may also be useful for dissolving or inhibiting formation of thromboses and for treatment and prevention of conditions resulting therefrom (such as, for example, infarction of cardiac and central nervous system vessels (e.g., stroke).

The activity of a protein of the invention may, among other means, be measured by the following methods:

Assay for hemostatic and thrombolytic activity include, without limitation, those described in: Linet et al., J. Clin. Pharmacol. 26:131-140, 1986; Burdick et al., Thrombosis Res. 45:413-419, 1987; Humphrey et al., Fibrinolysis 5:71-79 (1991); Schaub, Prostaglandins 35:467-474, 1988.

Receptor/Ligand Activity

A protein of the present invention may also demonstrate activity as receptors, receptor ligands or inhibitors or agonists of receptor/ligand interactions. Examples of such receptors and ligands include, without limitation, cytokine receptors and their ligands, receptor kinases and their ligands, receptor phosphatases and their ligands, receptors involved in cell-cell interactions and their ligands (including without limitation, cellular adhesion molecules (such as selectins, integrins and their ligands) and receptor/ligand pairs involved in antigen presentation, antigen recognition and development of cellular and humoral immune responses). Receptors and ligands are also useful for screening of potential peptide or small molecule inhibitors of the relevant receptor/ligand interaction. A protein of the present invention (including, without limitation, fragments of receptors and ligands) may themselves be useful as inhibitors of receptor/ligand interactions.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Suitable assays for receptor-ligand activity include without limitation those described in: Current Protocols in Immunology, Ed by J.E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W.Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 7.28, Measurement of Cellular Adhesion under static conditions 7.28.1-7.28.22), Takai et al., Proc. Natl. Acad. Sci. USA 84:6864-6868, 1987;

Bierer et al., J. Exp. Med. 168:1145-1156, 1988; Rosenstein et al., J. Exp. Med. 169:149-160 1989; Stoltenborg et al., J. Immunol. Methods 175:59-68, 1994; Stitt et al., Cell 80:661-670, 1995.

Anti-Inflammatory Activity

Proteins of the present invention may also exhibit anti-inflammatory activity. The anti-inflammatory activity may be achieved by providing a stimulus to cells involved in the inflammatory response, by inhibiting or promoting cell-cell interactions (such as, for example, cell adhesion), by inhibiting or promoting chemotaxis of cells involved in the inflammatory process, inhibiting or promoting cell extravasation, or by stimulating or suppressing production of other factors which more directly inhibit or promote an inflammatory response. Proteins exhibiting such activities can be used to treat inflammatory conditions including chronic or acute conditions), including without limitation inflammation associated with infection (such as septic shock, sepsis or systemic inflammatory response syndrome (SIRS)), ischemia-reperfusion injury, endotoxin lethality, arthritis, complement-mediated hyperacute rejection, nephritis, cytokine or chemokine-induced lung injury, inflammatory bowel disease, Crohn's disease or resulting from over production of cytokines such as TNF or IL-1. Proteins of the invention may also be useful to treat anaphylaxis and hypersensitivity to an antigenic substance or material.

Tumor Inhibition Activity

In addition to the activities described above for immunological treatment or prevention of tumors, a protein of the invention may exhibit other anti-tumor activities. A protein may inhibit tumor growth directly or indirectly (such as, for example, via ADCC). A protein may exhibit its tumor inhibitory activity by acting on tumor tissue or tumor precursor tissue, by inhibiting formation of tissues necessary to support tumor growth (such as, for example, by inhibiting angiogenesis), by causing production of other factors, agents or cell types which inhibit tumor growth, or by suppressing, eliminating or inhibiting factors, agents or cell types which promote tumor growth.

Other Activities

A protein of the invention may also exhibit one or more of the following additional activities or effects: inhibiting the growth, infection or function of, or killing, infectious

agents, including, without limitation, bacteria, viruses, fungi and other parasites; effecting (suppressing or enhancing) bodily characteristics, including, without limitation, height, weight, hair color, eye color, skin, fat to lean ratio or other tissue pigmentation, or organ or body part size or shape (such as, for example, breast augmentation or diminution, change in bone form or shape); effecting biorhythms or caricadic cycles or rhythms; effecting the fertility of male or female subjects; effecting the metabolism, catabolism, anabolism, processing, utilization, storage or elimination of dietary fat, lipid, protein, carbohydrate, vitamins, minerals, cofactors or other nutritional factors or component(s); effecting behavioral characteristics, including, without limitation, appetite, libido, stress, cognition (including cognitive disorders), depression (including depressive disorders) and violent behaviors; providing analgesic effects or other pain reducing effects; promoting differentiation and growth of embryonic stem cells in lineages other than hematopoietic lineages; hormonal or endocrine activity; in the case of enzymes, correcting deficiencies of the enzyme and treating deficiency-related diseases; treatment of hyperproliferative disorders (such as, for example, psoriasis); immunoglobulin-like activity (such as, for example, the ability to bind antigens or complement); and the ability to act as an antigen in a vaccine composition to raise an immune response against such protein or another material or entity which is cross-reactive with such protein.

ADMINISTRATION AND DOSING

A protein of the present invention (from whatever source derived, including without limitation from recombinant and non-recombinant sources) may be used in a pharmaceutical composition when combined with a pharmaceutically acceptable carrier. Such a composition may also contain (in addition to protein and a carrier) diluents, fillers, salts, buffers, stabilizers, solubilizers, and other materials well known in the art. The term "pharmaceutically acceptable" means a non-toxic material that does not interfere with the effectiveness of the biological activity of the active ingredient(s). The characteristics of the carrier will depend on the route of administration. The pharmaceutical composition of the invention may also contain cytokines, lymphokines, or other hematopoietic factors such as M-CSF, GM-CSF, TNF, IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-11, IL-12, IL-13, IL-14, IL-15, IFN, TNF0, TNF1, TNF2, G-CSF, Meg-CSF, thrombopoietin, stem cell factor, and erythropoietin. The pharmaceutical composition may further contain other agents which either enhance the activity of the protein or compliment its activity or

use in treatment. Such additional factors and/or agents may be included in the pharmaceutical composition to produce a synergistic effect with protein of the invention, or to minimize side effects. Conversely, protein of the present invention may be included in formulations of the particular cytokine, lymphokine, other hematopoietic factor, thrombolytic or anti-thrombotic factor, or anti-inflammatory agent to minimize side effects of the cytokine, lymphokine, other hematopoietic factor, thrombolytic or anti-thrombotic factor, or anti-inflammatory agent.

A protein of the present invention may be active in multimers (e.g., heterodimers or homodimers) or complexes with itself or other proteins. As a result, pharmaceutical compositions of the invention may comprise a protein of the invention in such multimeric or complexed form.

The pharmaceutical composition of the invention may be in the form of a complex of the protein(s) of present invention along with protein or peptide antigens. The protein and/or peptide antigen will deliver a stimulatory signal to both B and T lymphocytes. B lymphocytes will respond to antigen through their surface immunoglobulin receptor. T lymphocytes will respond to antigen through the T cell receptor (TCR) following presentation of the antigen by MHC proteins. MHC and structurally related proteins including those encoded by class I and class II MHC genes on host cells will serve to present the peptide antigen(s) to T lymphocytes. The antigen components could also be supplied as purified MHC-peptide complexes alone or with co-stimulatory molecules that can directly signal T cells. Alternatively antibodies able to bind surface immunolgobulin and other molecules on B cells as well as antibodies able to bind the TCR and other molecules on T cells can be combined with the pharmaceutical composition of the invention.

The pharmaceutical composition of the invention may be in the form of a liposome in which protein of the present invention is combined, in addition to other pharmaceutically acceptable carriers, with amphipathic agents such as lipids which exist in aggregated form as micelles, insoluble monolayers, liquid crystals, or lamellar layers in aqueous solution. Suitable lipids for liposomal formulation include, without limitation, monoglycerides, diglycerides, sulfatides, lysolecithin, phospholipids, saponin, bile acids, and the like. Preparation of such liposomal formulations is within the level of skill in the art, as disclosed, for example, in U.S. Patent No. 4,235,871; U.S. Patent No. 4,501,728; U.S. Patent No. 4,837,028; and U.S. Patent No. 4,737,323, all of which are incorporated herein by reference.

As used herein, the term "therapeutically effective amount" means the total amount of each active component of the pharmaceutical composition or method that is sufficient to show a meaningful patient benefit, i.e., treatment, healing, prevention or amelioration of the relevant medical condition, or an increase in rate of treatment, healing, prevention or amelioration of such conditions. When applied to an individual active ingredient, administered alone, the term refers to that ingredient alone. When applied to a combination, the term refers to combined amounts of the active ingredients that result in the therapeutic effect, whether administered in combination, serially or simultaneously.

In practicing the method of treatment or use of the present invention, a therapeutically effective amount of protein of the present invention is administered to a mammal having a condition to be treated. Protein of the present invention may be administered in accordance with the method of the invention either alone or in combination with other therapies such as treatments employing cytokines, lymphokines or other hematopoietic factors. When co-administered with one or more cytokines, lymphokines or other hematopoietic factors, protein of the present invention may be administered either simultaneously with the cytokine(s), lymphokine(s), other hematopoietic factor(s), thrombolytic or anti-thrombotic factors, or sequentially. If administered sequentially, the attending physician will decide on the appropriate sequence of administering protein of the present invention in combination with cytokine(s), lymphokine(s), other hematopoietic factor(s), thrombolytic or anti-thrombotic factors.

Administration of protein of the present invention used in the pharmaceutical composition or to practice the method of the present invention can be carried out in a variety of conventional ways, such as oral ingestion, inhalation, topical application or cutaneous, subcutaneous, intraperitoneal, parenteral or intravenous injection. Intravenous administration to the patient is preferred.

When a therapeutically effective amount of protein of the present invention is administered orally, protein of the present invention will be in the form of a tablet, capsule, powder, solution or elixir. When administered in tablet form, the pharmaceutical composition of the invention may additionally contain a solid carrier such as a gelatin or an adjuvant. The tablet, capsule, and powder contain from about 5 to 95% protein of the present invention, and preferably from about 25 to 90% protein of the present invention. When administered in liquid form, a liquid carrier such as water, petroleum, oils of animal or plant origin such as peanut oil, mineral oil, soybean oil, or sesame oil, or synthetic oils may be added. The liquid form of the pharmaceutical composition may further contain

physiological saline solution, dextrose or other saccharide solution, or glycols such as ethylene glycol, propylene glycol or polyethylene glycol. When administered in liquid form, the pharmaceutical composition contains from about 0.5 to 90% by weight of protein of the present invention, and preferably from about 1 to 50% protein of the present invention.

When a therapeutically effective amount of protein of the present invention is administered by intravenous, cutaneous or subcutaneous injection, protein of the present invention will be in the form of a pyrogen-free, parenterally acceptable aqueous solution. The preparation of such parenterally acceptable protein solutions, having due regard to pH, isotonicity, stability, and the like, is within the skill in the art. A preferred pharmaceutical composition for intravenous, cutaneous, or subcutaneous injection should contain, in addition to protein of the present invention, an isotonic vehicle such as Sodium Chloride Injection, Ringer's Injection, Dextrose Injection, Dextrose and Sodium Chloride Injection, Lactated Ringer's Injection, or other vehicle as known in the art. The pharmaceutical composition of the present invention may also contain stabilizers, preservatives, buffers, antioxidants, or other additives known to those of skill in the art.

The amount of protein of the present invention in the pharmaceutical composition of the present invention will depend upon the nature and severity of the condition being treated, and on the nature of prior treatments which the patient has undergone. Ultimately, the attending physician will decide the amount of protein of the present invention with which to treat each individual patient. Initially, the attending physician will administer low doses of protein of the present invention and observe the patient's response. Larger doses of protein of the present invention may be administered until the optimal therapeutic effect is obtained for the patient, and at that point the dosage is not increased further. It is contemplated that the various pharmaceutical compositions used to practice the method of the present invention should contain about 0.01 μg to about 100 mg (preferably about 0.1μg to about 10 mg, more preferably about 0.1 μg to about 1 mg) of protein of the present invention per kg body weight.

The duration of intravenous therapy using the pharmaceutical composition of the present invention will vary, depending on the severity of the disease being treated and the condition and potential idiosyncratic response of each individual patient. It is contemplated that the duration of each application of the protein of the present invention will be in the range of 12 to 24 hours of continuous intravenous administration. Ultimately the attending

physician will decide on the appropriate duration of intravenous therapy using the pharmaceutical composition of the present invention.

Protein of the invention may also be used to immunize animals to obtain polyclonal and monoclonal antibodies which specifically react with the protein. Such antibodies may be obtained using either the entire protein or fragments thereof as an immunogen. The peptide immunogens additionally may contain a cysteine residue at the carboxyl terminus, and are conjugated to a hapten such as keyhole limpet hemocyanin (KLH). Methods for synthesizing such peptides are known in the art, for example, as in R.P. Merrifield, J. Amer.Chem. Soc. 85, 2149-2154 (1963); J.L. Krstenansky, *et al.*, FEBS Lett. 211, 10 (1987). Monoclonal antibodies binding to the protein of the invention may be useful diagnostic agents for the immunodetection of the protein. Neutralizing monoclonal antibodies binding to the protein may also be useful therapeutics for both conditions associated with the protein and also in the treatment of some forms of cancer where abnormal expression of the protein is involved. In the case of cancerous cells or leukemic cells, neutralizing monoclonal antibodies against the protein may be useful in detecting and preventing the metastatic spread of the cancerous cells, which may be mediated by the protein.

For compositions of the present invention which are useful for bone, cartilage, tendon or ligament regeneration, the therapeutic method includes administering the composition topically, systematically, or locally as an implant or device. When administered, the therapeutic composition for use in this invention is, of course, in a pyrogen-free, physiologically acceptable form. Further, the composition may desirably be encapsulated or injected in a viscous form for delivery to the site of bone, cartilage or tissue damage. Topical administration may be suitable for wound healing and tissue repair. Therapeutically useful agents other than a protein of the invention which may also optionally be included in the composition as described above, may alternatively or additionally, be administered simultaneously or sequentially with the composition in the methods of the invention. Preferably for bone and/or cartilage formation, the composition would include a matrix capable of delivering the protein-containing composition to the site of bone and/or cartilage damage, providing a structure for the developing bone and cartilage and optimally capable of being resorbed into the body. Such matrices may be formed of materials presently in use for other implanted medical applications.

The choice of matrix material is based on biocompatibility, biodegradability, mechanical properties, cosmetic appearance and interface properties. The particular

application of the compositions will define the appropriate formulation. Potential matrices for the compositions may be biodegradable and chemically defined calcium sulfate, tricalciumphosphate, hydroxyapatite, polylactic acid, polyglycolic acid and polyanhydrides. Other potential materials are biodegradable and biologically well-defined, such as bone or dermal collagen. Further matrices are comprised of pure proteins or extracellular matrix components. Other potential matrices are nonbiodegradable and chemically defined, such as sintered hydroxapatite, bioglass, aluminates, or other ceramics. Matrices may be comprised of combinations of any of the above mentioned types of material, such as polylactic acid and hydroxyapatite or collagen and tricalciumphosphate. The bioceramics may be altered in composition, such as in calcium-aluminate-phosphate and processing to alter pore size, particle size, particle shape, and biodegradability.

Presently preferred is a 50:50 (mole weight) copolymer of lactic acid and glycolic acid in the form of porous particles having diameters ranging from 150 to 800 microns. In some applications, it will be useful to utilize a sequestering agent, such as carboxymethyl cellulose or autologous blood clot, to prevent the protein compositions from disassociating from the matrix.

A preferred family of sequestering agents is cellulosic materials such as alkylcelluloses(including hydroxyalkylcelluloses),including methylcellulose, ethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropyl-methylcellulose, and carboxymethylcellulose,the most preferred being cationic salts of carboxymethylcellulose (CMC). Other preferred sequestering agents include hyaluronic acid, sodium alginate, poly(ethylene glycol), polyoxyethylene oxide, carboxyvinyl polymer and poly(vinyl alcohol). The amount of sequestering agent useful herein is 0.5-20 wt%, preferably 1-10 wt% based on total formulation weight, which represents the amount necessary to prevent desorbtion of the protein from the polymer matrix and to provide appropriate handling of the composition, yet not so much that the progenitor cells are prevented from infiltrating the matrix, thereby providing the protein the opportunity to assist the osteogenic activity of the progenitor cells.

In further compositions, proteins of the invention may be combined with other agents beneficial to the treatment of the bone and/or cartilage defect, wound, or tissue in question. These agents include various growth factors such as epidermal growth factor (EGF), platelet derived growth factor (PDGF), transforming growth factors (TGF-α and TGF-β), and insulin-like growth factor (IGF).

The therapeutic compositions are also presently valuable for veterinary applications. Particularly domestic animals and thoroughbred horses, in addition to humans, are desired patients for such treatment with proteins of the present invention.

The dosage regimen of a protein-containing pharmaceutical composition to be used in tissue regeneration will be determined by the attending physician considering various factors which modify the action of the proteins, e.g., amount of tissue weight desired to be formed, the site of damage, the condition of the damaged tissue, the size of a wound, type of damaged tissue (e.g., bone), the patient's age, sex, and diet, the severity of any infection, time of administration and other clinical factors. The dosage may vary with the type of matrix used in the reconstitution and with inclusion of other proteins in the pharmaceutical composition. For example, the addition of other known growth factors, such as IGF I (insulin like growth factor I), to the final composition, may also effect the dosage. Progress can be monitored by periodic assessment of tissue/bone growth and/or repair, for example, X-rays, histomorphometric determinations and tetracycline labeling.

Polynucleotides of the present invention can also be used for gene therapy. Such polynucleotides can be introduced either *in vivo* or *ex vivo* into cells for expression in a mammalian subject. Polynucleotides of the invention may also be administered by other known methods for introduction of nucleic acid into a cell or organism (including, without limitation, in the form of viral vectors or naked DNA).

Cells may also be cultured *ex vivo* in the presence of proteins of the present invention in order to proliferate or to produce a desired effect on or activity in such cells. Treated cells can then be introduced *in vivo* for therapeutic purposes.

Patent and literature references cited herein are incorporated by reference as if fully set forth.

SEQUENCE LISTING

(1) GENERAL INFORMATION:

(i) APPLICANT: Jacobs, Kenneth
McCoy, John
LaVallie, Edward
Racie, Lisa
Merberg, David
Treacy, Maurice
Spaulding, Vicky

(ii) TITLE OF INVENTION: SECRETED PROTEINS AND POLYNUCLEOTIDES ENCODING THEM

(iii) NUMBER OF SEQUENCES: 25

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(v) COMPUTER READABLE FORM:
(A) MEDIUM TYPE: Floppy disk
(B) COMPUTER: IBM PC compatible
(C) OPERATING SYSTEM: PC-DOS/MS-DOS
(D) SOFTWARE: PatentIn Release #1.0, Version #1.30

(vi) CURRENT APPLICATION DATA:
(A) APPLICATION NUMBER:
(B) FILING DATE:
(C) CLASSIFICATION:

(viii) ATTORNEY/AGENT INFORMATION:
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(2) INFORMATION FOR SEQ ID NO:1:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 162 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:

GAATTCGGCC AAAGAGGCCT AGTGATATTA TAGTGTAGTT TTTTAGATGT TACCATTGGG 60

AGAAACTGAG TAAAGAAGAT GTGGGATCTT TCTTTAGTAT TTCTTAGAAC TGCATGTGAA 120

TCTACAACTA GCTCAAAATA AAAAGTTTAA TTATAAATAA AA 162

(2) INFORMATION FOR SEQ ID NO:2:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1014 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:

TTTGGGCTCA GTGAATTTGC TTCTTCAGGA GGGTAATTTT CTCTTCTTTC TCTGCTAAGC 60

TGTTTAACAG TAGTTGCCCT GCCTAATGGG CTTCATCCAT CCATTTCTCT CAGATTATTT 120

TCATGATGCA CTAGGATGAA GCACACCCTT TCTCCTAGTC TTGAGGAAAC GTCGATATTC 180

AGAATATTTA AACGCAGGCA CTGACCAATC AGAAGAGTTT CTGGCCAACG TTCCACACTT 240

GAGGGAAATG ACATTATCTG AGCCCTGAAG AAAAACGTTG TAGATATTCT CCAGATCAAA 300

GCATCGACAG GAAGATTTTA GATGTTGAAG TTCGTAATAT TTCCTAAAGC AGGTTGTGTG 360

CATTCAAARG AGMAKTCTAT TAAAGCTACC YTMNWTTGGC GCTTATTTTT CTTAATCATG 420

TTTCTGACAA TCATAGTGTG TGGAGRKGGT TGCTGCTTTA AGYGCAATAA GAGCTAWCTG 480

CCATCAAGAG CCATCAGTAT GTCTTCGAGC TGCATGCCCA GAAAGCTGGA TTGTTTTTCA 540

AACGAAAGTG TYTCTATTTT TCTGATGACR CCAAGAAACT GGACATCAAG TCAGAGGKKT 600

TGTGACTCAC AAGATGCTGA TCTTGCTCAG GTTGAAAGCT TCCAGGAACT GAATTTCCTG 660

TTGAGAKATA AAGGCCCATC TGATCACTGG ATTGGGCTGA GCANAGAACA NGGCCAACCA 720

TGGAAATGGA TAAATGGTAC TGAATGGACA ANACAGTTTC CTATCCTGGG AGCAGGANAN 780

TGTGCCTATT TGAATGACAA AGGTGCCAGT AGTGCCAGGC ACTACACAGA GAGGAANTGG 840

ATTTGTNCCA AATCANATNT NCTTNTCTAN ATGTTACAGC AAAGCCCCAA CTAATCTTTA 900

NAAGCATATT GGAACTGATA ACTCCATTTT AAAATGAGCA AANANTTTAT TTCTTATNCC 960

AACNGGTATA TGAAAATATG CTCNATNTCA CTAATAACTG GGAAAATAAC CNTT 1014

(2) INFORMATION FOR SEQ ID NO:3:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 338 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:3:

```
Phe Gly Leu Ser Glu Phe Ala Ser Ser Gly Gly Xaa Phe Ser Leu Leu
1               5                  10                  15

Ser Leu Leu Ser Cys Leu Thr Val Val Ala Leu Pro Asn Gly Leu His
            20                  25                  30

Pro Ser Ile Ser Leu Arg Leu Phe Ser Xaa Cys Thr Arg Met Lys His
        35                  40                  45

Thr Leu Ser Pro Ser Leu Glu Glu Thr Ser Ile Phe Arg Ile Phe Lys
    50                  55                  60

Arg Arg His Xaa Pro Ile Arg Arg Val Ser Gly Gln Arg Ser Thr Leu
65                  70                  75                  80

Glu Gly Asn Asp Ile Ile Xaa Ala Leu Lys Lys Asn Val Val Asp Ile
                85                  90                  95

Leu Gln Ile Lys Ala Ser Thr Gly Arg Phe Xaa Met Leu Lys Phe Val
            100                 105                 110

Ile Phe Pro Lys Ala Gly Cys Val His Ser Lys Glu Xaa Ser Ile Lys
        115                 120                 125

Ala Thr Xaa Xaa Trp Arg Leu Phe Phe Leu Ile Met Phe Leu Thr Ile
    130                 135                 140

Ile Val Cys Gly Xaa Gly Cys Cys Phe Lys Xaa Asn Lys Ser Xaa Leu
145                 150                 155                 160

Pro Ser Arg Ala Ile Ser Met Ser Ser Ser Cys Met Pro Arg Lys Leu
                165                 170                 175

Asp Cys Phe Ser Asn Glu Ser Val Ser Ile Phe Leu Met Thr Pro Arg
            180                 185                 190

Asn Trp Thr Ser Ser Gln Arg Xaa Cys Asp Ser Gln Asp Ala Asp Leu
        195                 200                 205

Ala Gln Val Glu Ser Phe Gln Glu Leu Asn Phe Leu Leu Arg Xaa Lys
    210                 215                 220

Gly Pro Ser Asp His Trp Ile Gly Leu Ser Xaa Glu Xaa Gly Gln Pro
225                 230                 235                 240

Trp Lys Trp Ile Asn Gly Thr Glu Trp Thr Xaa Gln Phe Pro Ile Leu
                245                 250                 255

Gly Ala Gly Xaa Cys Ala Tyr Leu Asn Asp Lys Gly Ala Ser Ser Ala
            260                 265                 270

Arg His Tyr Thr Glu Arg Xaa Trp Ile Cys Xaa Lys Ser Xaa Xaa Leu
        275                 280                 285

Xaa Xaa Met Leu Gln Gln Ser Pro Asn Xaa Ser Leu Xaa Ala Tyr Trp
```

290 295 300

Asn Xaa Xaa Leu His Phe Lys Met Ser Lys Xaa Phe Ile Ser Tyr Xaa
305 310 315 320

Asn Xaa Tyr Met Lys Ile Cys Ser Xaa Ser Leu Ile Thr Gly Lys Ile
325 330 335

Thr Xaa

(2) INFORMATION FOR SEQ ID NO:4:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 177 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:4:

ATATGCTCAA TATCACTAAT AACTGGGAAA TACAAATCAA AATCATAGTA AAATATTACC 60

TGTTTTCATG GTGCTAATAT TACCTGTTCT CCCACTGCTA ATGACATACC CGAGACTGAG 120

TAATTTATAA ATAAAAGAGA TTTAATTGAA AAAAAAAAAA AAAAAAAAAA AAAAAAA 177

(2) INFORMATION FOR SEQ ID NO:5:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 325 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:5:

TCTTTCTTTT TTCTCCCCTT TACTCTTTGG GTGGTGTTGC TTTTCCTTTC CTTTTCCCTT 60

TGARATTTTT TTGTTGTTGT TTCCTTTTTG TATTTTACTG ATATCACCAG NATAGTTTAC 120

TCTCCTTCTA GCTTTCTGCT TACCGCACAC TGGATAACAC ACACATACAC ACCCACAAAA 180

ATGCTCATGA ACCCAATCCG GAGAAGGTTC CAGCAGGTCC CCCACCCTCC CCTCCTCCTC 240

CTACTTCTCC TCTTGACAGC GAGGACAGGA GGGGGACAAG GGGACACCTG GGCAGACCCG 300

CCGGCTCTCC CCCCACCCCA CCCCG 325

(2) INFORMATION FOR SEQ ID NO:6:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 48 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:6:

```
Met Leu Met Asn Pro Ile Arg Arg Arg Phe Gln Gln Val Pro His Pro
1               5                  10                  15

Pro Leu Leu Leu Leu Leu Leu Leu Leu Thr Ala Arg Thr Gly Gly Gly
            20                  25                  30

Gln Gly Asp Thr Trp Ala Asp Pro Pro Ala Leu Pro Pro Pro His Pro
        35                  40                  45
```

(2) INFORMATION FOR SEQ ID NO:7:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 101 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:7:

```
TATGTTTTGA TTTTTAAAAA AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA      60

AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA A                        101
```

(2) INFORMATION FOR SEQ ID NO:8:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 522 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:8:

```
GAATTCGGCA AAGAGCTANG AATTCGTTAT CCGCGATGCG TTTCCTGGCA GCTACATTCC      60

TGCTCCTGGC GCTCAGCACC GCTGCCCAGG CCGAACCGGT GCAGTTCAAG GACTGCGGTT     120

CTGTGGATGG AGTTATAAAG GAAGTGAATG TGAGCCCATG CCCCACCCAA CCCTGCCAGC     180
```

TGAGCAAAGG ACAGTCTTAC AGCGTCAATG TCACCTTCAC CAGCAATATT CAGTCTAAAA 240

GCAGCAAGGC CGTGGTGCAT GGCATCCTGA TGGGCGTCCC AGTTCCCTTT CCCATTCCTG 300

AGCCTGATGG TTGTAAGAGT GGAATTAACT GCCCTATCCA AAAAGACAAG ACCTATAGCT 360

ACCTGAATAA ACTACCAGTG AAAAGCGAAT ATCCCTCTAT AAAACTGGTG GTGGAGTGGC 420

AACTTCAGGA TGACAAAAAC CAAATCTCTT CTGCTGGGAA ATCCCAGTNC AGATCGTTTC 480

TCATCTCTAA GTGCCTCATT GAGTTCGGTG CATCTGGGCC AA 522

(2) INFORMATION FOR SEQ ID NO:9:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 162 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:9:

Met Arg Phe Leu Ala Ala Thr Phe Leu Leu Leu Ala Leu Ser Thr Ala
1 5 10 15

Ala Gln Ala Glu Pro Val Gln Phe Lys Asp Cys Gly Ser Val Asp Gly
20 25 30

Val Ile Lys Glu Val Asn Val Ser Pro Cys Pro Thr Gln Pro Cys Gln
35 40 45

Leu Ser Lys Gly Gln Ser Tyr Ser Val Asn Val Thr Phe Thr Ser Asn
50 55 60

Ile Gln Ser Lys Ser Ser Lys Ala Val Val His Gly Ile Leu Met Gly
65 70 75 80

Val Pro Val Pro Phe Pro Ile Pro Glu Pro Asp Gly Cys Lys Ser Gly
85 90 95

Ile Asn Cys Pro Ile Gln Lys Asp Lys Thr Tyr Ser Tyr Leu Asn Lys
100 105 110

Leu Pro Val Lys Ser Glu Tyr Pro Ser Ile Lys Leu Val Val Glu Trp
115 120 125

Gln Leu Gln Asp Asp Lys Asn Gln Ile Ser Ser Ala Gly Lys Ser Gln
130 135 140

Xaa Arg Ser Phe Leu Ile Ser Lys Cys Leu Ile Glu Phe Gly Ala Ser
145 150 155 160

Gly Pro

(2) INFORMATION FOR SEQ ID NO:10:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 259 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:10:

TTTGTAGCAG AAAATGNGCT CCGGGNGGNT GGTTTTCAGG GGGTGTNTCA AGTTTNTTTT 60

TCTGTTTTAG GGGGNTTCAT TAAANGCAGC ANTTGGTTAG CAGANGTTTA ATTTTTTTTT 120

TAACAANATT AAATTGNGGC CTCTTTTNAC ANCTGGNAAT TNANTTTTGN ATAAATAAAA 180

AATNGTTTGT TTTGTCCAAA AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA 240

AAAAAAAAAA AAAAAAAAG 259

(2) INFORMATION FOR SEQ ID NO:11:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 499 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:11:

AGCAANAAAC CAGTCAACTC ATGCACNCGA GCGGTNCANG AAACCAACAA AAATAACTCT 60

GAGAGCATAG AATGCAGAAA AATAACAATG GATCTCAATT TCAACCANTC CAGAAAANAT 120

ATCTCTATCA CTGTNCCATC CAAAACCCAA ACAATGTCAC CACACATCAA GTCAGTTGAC 180

GACGTTGTGG TACTTGGCAT GAATCTCAGC AAGTTTAACA AACTTACTCA GTTTTTCATA 240

TGTGTTGCTG GAGTTTTTGT ATTTTACCTA ATTTATGGGT ATTTACAGGA ATTAATATTT 300

TCAGTGGAGG GTTTTAAGTC CTGTGGCTGG TACCTTACCT TAGTGCAGTT TGCCTTTTAC 360

TCCATATTTG GCCTAATAGA ACTTCAGCTT ATTCAGGACA AAAGGAGGAG AATACCAGGA 420

AAAAACCTAC ATGATAATAG CTTTTCTAAC TGTGGGTACT ATGGGGNNGG CAAACACTTC 480

CTTGGGCTAC CTGAATTAC 499

(2) INFORMATION FOR SEQ ID NO:12:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 137 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:12:

Met Asp Leu Asn Phe Asn Xaa Ser Arg Lys Xaa Ile Ser Ile Thr Val
1 5 10 15

Pro Ser Lys Thr Gln Thr Met Ser Pro His Ile Lys Ser Val Asp Asp
20 25 30

Val Val Val Leu Gly Met Asn Leu Ser Lys Phe Asn Lys Leu Thr Gln
35 40 45

Phe Phe Ile Cys Val Ala Gly Val Phe Val Phe Tyr Leu Ile Tyr Gly
50 55 60

Tyr Leu Gln Glu Leu Ile Phe Ser Val Glu Gly Phe Lys Ser Cys Gly
65 70 75 80

Trp Tyr Leu Thr Leu Val Gln Phe Ala Phe Tyr Ser Ile Phe Gly Leu
85 90 95

Ile Glu Leu Gln Leu Ile Gln Asp Lys Arg Arg Arg Ile Pro Gly Lys
100 105 110

Asn Leu His Asp Asn Ser Phe Ser Asn Cys Gly Tyr Tyr Gly Xaa Gly
115 120 125

Lys His Phe Leu Gly Leu Pro Glu Leu
130 135

(2) INFORMATION FOR SEQ ID NO:13:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 438 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:13:

ACTTTCCAAA GGGATGATAA AACCAAAGAA TTGGAGGCAT TGTATCCCAT TTGTGGACAG 60

ATTTCATATG AAGTTGTTTT GCGGTGTCAG CCTTTTTTTC AGAGCATTTG TTTGACTGAC 120

TTCCAAAGCA ATCAAGAGAG CCACGTCTAG CAGACTTTAC AATAAAATGT CAATATGAAG 180

GACTGTAATT CCTAGCAGTT TATTGAGAAT TTCACTGGAA ATGGACCATG TGTTGCAAGA 240

CTAATTGGCT ATAATTATAT CCTATCAAAG AAATCGATAC GTAATAGCAG ATTGTTTTAT 300

ATTCATTCCA TTTTGATGGT GTTATTTAAA TTGTTCTCTG TTATAAGAGT AAACTGATGA 360

GTTGAAGTCT GGAGAGAATA ACATTCATTA TAAATAAAAT TATTCTGTGT CTTTTTCAAA 420

AAAAAAAAAA AAAAAAAA 438

(2) INFORMATION FOR SEQ ID NO:14:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 479 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:14:

GTGGGATTTA ATTAAGAATT NGGCCCAAAG AGGCCTAACA GGATCAACAC ATTTCATCTG 60

GGCTTCTTAA ATCTAAATCT TTAAAATGAC TAAGTTTTCT TCCTTTTCTC TGTTTTTCCT 120

AATAGTTGGG GCTTAATATG ACTCATGTGT GTTTCAATAT GGAAATTATT GGAGGGAAAG 180

AAGTGTCACC TCATTCCAGG CCANTTATGG CCTCCATCCA GTATGGCGGA CATCACGTTT 240

GTGGAGGTGT TCTGATTGAT CCACAGTGGG TGCTGACAGC AGCCCACTGC CAATATCGGT 300

TTACCAAAGG CCAGTCTCCC ACTGTGGTTT TAGGCGCACA CTCTCTCTCA AAGAATGAGG 360

CCTCCAAACA AACACTGGAG ATCAAAAAAT TTATACCATT CTCAAGAGTT ACATCAGATC 420

CTCAATCCAA TGATATCATG CTGGTTAAGC NTCAAACAGC CGCCAAACTC AATAAACAT 479

(2) INFORMATION FOR SEQ ID NO:15:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 114 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:15:

Met Thr His Val Cys Phe Asn Met Glu Ile Ile Gly Gly Lys Glu Val
1 5 10 15

Ser Pro His Ser Arg Pro Xaa Met Ala Ser Ile Gln Tyr Gly Gly His
20 25 30

His Val Cys Gly Gly Val Leu Ile Asp Pro Gln Trp Val Leu Thr Ala
35 40 45

Ala His Cys Gln Tyr Arg Phe Thr Lys Gly Gln Ser Pro Thr Val Val
50 55 60

Leu Gly Ala His Ser Leu Ser Lys Asn Glu Ala Ser Lys Gln Thr Leu
65 70 75 80

Glu Ile Lys Lys Phe Ile Pro Phe Ser Arg Val Thr Ser Asp Pro Gln
85 90 95

Ser Asn Asp Ile Met Leu Val Lys Xaa Gln Thr Ala Ala Lys Leu Asn
100 105 110

Lys His

(2) INFORMATION FOR SEQ ID NO:16:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 173 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:16:

GCAGGTTAGA GTTGGTGTAG TAAAGCAGAG CACATATGGG TCCATTTTGC ACTTGTAAGT 60

CATTTTATTA AGGAATCAAG TTCTTTTTCA CTTGTATCAC TGATGTATTT CTACCATGCT 120

GGTTTTATTC TAAATAAAAT TTAGAAGACT CTCAAAAAAA AAAAAAAAAA AAA 173

(2) INFORMATION FOR SEQ ID NO:17:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 461 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:17:

CGATAATCTT CTTCCATTTG NGGGGAAATT TATTGCATCC TTCTTTAAAC CGGGGTTTGA 60

GAAGTATNAT AACTTGGATC TNTNTCGGNA TCTCTTAAAT ATTCCAGGAC CAATTGACAN 120

NCCATCTCGA ATTCGGCCAA AGAGGCCTAG ATGATGATAT GTTTAACCAC CAAGTTCCTT 180

ATTTGTGGCT GATTTACTGC CTTTGTCATC CTCTTCAATC AAGTATTAAA GAAACAGTGG 240

AGGCATATGA GGCAGCATTA GGGGTGGCTA TGAGATGTGA TATAGTACAG AAGATATGGA 300

TGGATTATCT TGTCTTTGCA AATAATAGAG CTGCTGGATC CAGAAACAAA GTTCAAGAAT 360

TCAAATTTTT TACTGATTTA GTGAATAGAT GTTTGGTTAC AGTCCCTGCC CGATACCCCA 420

TTCCTTTTAG CAGTGCTGAT TACTGGTCCA ACTATGAATT T 461

(2) INFORMATION FOR SEQ ID NO:18:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 101 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:18:

Met Phe Asn His Gln Val Pro Tyr Leu Trp Leu Ile Tyr Cys Leu Cys
1 5 10 15

His Pro Leu Gln Ser Ser Ile Lys Glu Thr Val Glu Ala Tyr Glu Ala
20 25 30

Ala Leu Gly Val Ala Met Arg Cys Asp Ile Val Gln Lys Ile Trp Met
35 40 45

Asp Tyr Leu Val Phe Ala Asn Asn Arg Ala Ala Gly Ser Arg Asn Lys
50 55 60

Val Gln Glu Phe Lys Phe Phe Thr Asp Leu Val Asn Arg Cys Leu Val
65 70 75 80

Thr Val Pro Ala Arg Tyr Pro Ile Pro Phe Ser Ser Ala Asp Tyr Trp
85 90 95

Ser Asn Tyr Glu Phe
100

(2) INFORMATION FOR SEQ ID NO:19:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 318 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:19:

TTTTTTGAGA TTCTTCATTT CGGGATTTTA AAACNATAGC AGNCCATCTT AAGGAAAGTG 60

TANCTNCCAT GGCCACAAGT CTGCTAGTTG CACTTGAATG CTCTATCNGG GTTGTTTATT 120

ACCCTTTCNA CGTTCTGGAC TCCTTTCCGA GACTGTTTAA CTTGNAGATT AAAGAAACTA 180

TTCCAAATGC CAGTGCATCA GNACCTAAGA GTGGGCAAAT ATTATGTGCA ATTTTTTTGT 240

AAAGAAATTT TAATTTATAA TAAAGTTTAA CAGTTTAAAG GNCCCCAAAA AAAAAAAAAA 300

AAAAAAAAAA AAAAAAAA 318

(2) INFORMATION FOR SEQ ID NO:20:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 27 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "oligonucleotide"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:20:

CCATCAGTAT GTCTTCGAGC TGCATGC 27

(2) INFORMATION FOR SEQ ID NO:21:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 27 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "oligonucleotide"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:21:

ATGCTCATGA ACCCAATCCG GAGAAGG 27

(2) INFORMATION FOR SEQ ID NO:22:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 27 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "oligonucleotide"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:22:

GCTCAGGAAT GGGAAAGGGA ACTGGGA 27

(2) INFORMATION FOR SEQ ID NO:23:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "oligonucleotide"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:23:

CATGATAATA GCTTTTCTAA CTGTGGGTAC 30

(2) INFORMATION FOR SEQ ID NO:24:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 27 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "oligonucleotide"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:24:

GTGGTTTTAG GCGCACACTC TCTCTCA 27

(2) INFORMATION FOR SEQ ID NO:25:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 45 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "oligonucleotide"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:25:

AAAGGCAGTA AATCAGCCAC AAATAAGGAA CTTGGTGGTT AAACA 45

(2) INFORMATION FOR SEQ ID NO:26:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1560 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:26:

GTGATATTAT AGTGTAGTTT TTAGATGTT ACCATTGGGA GAAACTGAGT AAAGAAGATG 60

TGGGATCTTT CTTTAGTATT TCTTAGAACT GCATGTGAAT CTACAACTAG CTCAAAATAA 120

AAAGTTTAAT TATAAAATAA AAGCTACATG AAATGAAGCA AAAAATAATT CACCCTTGTC 180

ACGCACACAG AGTCAGAGAC TGTAACATAA TTTGCAGGAT CTAGAGCAGA ATACAAATGT 240

AAAACATCTT GTTAAAAAAT TATTAATAAT TTTGAGACAT TGATAAAGCA TTAAGCCGCC 300

TGTGGGGCCC TTTAAGCATG ATAAACTGTG CTACCACACA GATTGCACAT TCACGTATCT 360

GGCCCTGCAA ATGGAATGAT TTTTGCCCAT GATCAATTCA CCATGGCCTC TTTGGGCTCA 420

GTGAATTTGC TTCTTCAGGA GGGTAATTTT CTCTTCTTTC TCTGCTAAGC TGTTTAACAG 480

TAGTTGCCCT GCCTAATGGG CTTCATCCAT CCATTTCTCT CAGATTATTT TCATGATGCA 540

CTAGGATGAA GCACACCCTT TCTCCTAGTC TTGAGGAAAC GTCGATATTC AGAATATTTA 600

AACGCAGGCA CTGACCAATC AGAAGAGTTT CTGGCCAACG TTCCACACTT GAGGGAAATG 660

ACATTATCTG AGCCCTGAAG AAAAACGTTG TAGATATTCT CCAGATCAAA GCATCGACAG 720

GAAGATTTTA GATGTTGAAG TTCGTAATAT TTCCTAAAGC AGGTTGTGTG CATTCAAAAG 780

AGCATTCTAT TAAAGCTACC TTAATTTGGC GCTTATTTTT CTTAATCATG TTTCTGACAA 840

TCATAGTGTG TGGAATGGTT GCTGCTTTAA GTGCAATAAG AGCTAACTGC CATCAAGAGC 900

CATCAGTATG TCTTCAAGCT GCATGCCCAG AAAGCTGGAT TGGTTTTCAA AGAAAGTGTT 960

TCTATTTTTC TGATGACACC AAGAACTGGA CATCAAGTCA GAGGTTTTGT GACTCACAAG 1020

ATGCTGATCT TGCTCAGGTT GAAAGCTTCC AGGAACTGAA TTTCCTGTTG AGATATAAAG 1080

GCCCATCTGA TCACTGGATT GGGCTGAGCA GAGAACAAGG CCAACCATGG AAATGGATAA 1140

ATGGTACTGA ATGGACAAGA CAGTTTCCTA TCCTGGGAGC AGGAGAGTGT GCCTATTTGA 1200

ATGACAAAGG TGCCAGTAGT GCCAGGCACT ACACAGAGAG GAAGTGGATT TGTTCCAAAT 1260

CAGATATACA TGTCTAGATG TTACAGCAAA GCCCCAACTA ATCTTTAGAA GCATATTGGA 1320

ACTGATAACT CCATTTTAAA ATGAGCAAAG AATTTATTTC TTATACCAAC AGGTATATGA 1380

AAATATGCTC AATATCACTA ATAACTGGGA AAATACAAAT CAAAATCATA GTAAAATATT 1440

ACCTGTTTTC ATGGTGCTAA TATTACCTGT TCTCCCACTG CTAATGACAT ACCCGAGACT 1500

GAGTAATTTA TAAATAAAAG AGATTTAATT GAAAAAAAAA AAAAAAAAAA AAAAAAAAAA 1560

(2) INFORMATION FOR SEQ ID NO:27:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 181 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:27:

```
Met Leu Lys Phe Val Ile Phe Pro Lys Ala Gly Cys Val His Ser Lys
1               5                  10                  15

Glu His Ser Ile Lys Ala Thr Leu Ile Trp Arg Leu Phe Phe Leu Ile
            20                  25                  30

Met Phe Leu Thr Ile Ile Val Cys Gly Met Val Ala Ala Leu Ser Ala
        35                  40                  45

Ile Arg Ala Asn Cys His Gln Glu Pro Ser Val Cys Leu Gln Ala Ala
    50                  55                  60

Cys Pro Glu Ser Trp Ile Gly Phe Gln Arg Lys Cys Phe Tyr Phe Ser
65                  70                  75                  80

Asp Asp Thr Lys Asn Trp Thr Ser Ser Gln Arg Phe Cys Asp Ser Gln
                85                  90                  95

Asp Ala Asp Leu Ala Gln Val Glu Ser Phe Gln Glu Leu Asn Phe Leu
            100                 105                 110

Leu Arg Tyr Lys Gly Pro Ser Asp His Trp Ile Gly Leu Ser Arg Glu
        115                 120                 125

Gln Gly Gln Pro Trp Lys Trp Ile Asn Gly Thr Glu Trp Thr Arg Gln
    130                 135                 140

Phe Pro Ile Leu Gly Ala Gly Glu Cys Ala Tyr Leu Asn Asp Lys Gly
145                 150                 155                 160

Ala Ser Ser Ala Arg His Tyr Thr Glu Arg Lys Trp Ile Cys Ser Lys
                165                 170                 175

Ser Asp Ile His Val
            180
```

(2) INFORMATION FOR SEQ ID NO:28:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 605 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:28:

```
TAGGACAAAA CAAAACATTT TCCCTTGGGG TTTTTTTTTT CTTTCTTTTT TCTCCCCTTT      60

ACTCTTTGGG TGGTGTTGCT TTTCCTTTCC TTTTCCCTTT GAGATTTTTT TGTTGTTGTT     120

TCCTTTTTGT ATTTTACTGA TATCACCAGG ATAGTTTACT CTCCTTCTAG CTTTCTGCTT     180
```

ACCGCACACT GGATAACACA CACATACACA CCCACAAAAA TGCTCATGAA CCCAATCCGG 240

AGAAGGTTCC AGCAGGTCCC CCACCCTCCC CTCCTCCTCC TACTTCTCCT CTTGACAGCG 300

AGGACAGGAG GGGGACAAGG GGACACCTGG GCAGACCCGC CGGCTCTCCC CCCACCCCAC 360

CCCGCCCCTC ACATCATACT CCAATCATAA CCTTGTATAT TACGCAGTCA TTTTGGTTTT 420

CGCGGACGCG CCTACCTAAG TACCATTTAC AGAAAGTGAC TCTGGCTGTC ATTATTTTGT 480

TTATTTGTTC CCTATGCAAA AAAAAAATGA AAATGAAAAA AGGGGGATTC CATAAAAGAT 540

TCAATAAAAG ACAAAAAAAA AGAAAAAAGA AAAAAATGTA TAAAAATTAA AAAAAAAAAA 600

AAAAA 605

(2) INFORMATION FOR SEQ ID NO:29:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 139 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:29:

Leu Ser Ala Tyr Arg Thr Leu Asp Asn Thr His Ile His Thr His Lys
1 5 10 15

Asn Ala His Glu Pro Asn Pro Glu Lys Val Pro Ala Gly Pro Pro Pro
20 25 30

Ser Pro Pro Pro Pro Thr Ser Pro Leu Asp Ser Glu Asp Arg Arg Gly
35 40 45

Thr Arg Gly His Leu Gly Arg Pro Ala Gly Ser Pro Pro Thr Pro Pro
50 55 60

Arg Pro Ser His His Thr Pro Ile Ile Thr Leu Tyr Ile Thr Gln Ser
65 70 75 80

Phe Trp Phe Ser Arg Thr Arg Leu Pro Lys Tyr His Leu Gln Lys Val
85 90 95

Thr Leu Ala Val Ile Ile Leu Phe Ile Cys Ser Leu Cys Lys Lys Lys
100 105 110

Met Lys Met Lys Lys Gly Gly Phe His Lys Arg Phe Asn Lys Arg Gln
115 120 125

Lys Lys Arg Lys Lys Lys Lys Met Tyr Lys Asn
130 135

(2) INFORMATION FOR SEQ ID NO:30:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 863 base pairs

(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:30:

GGAACTTCGT TATCCGCGAT GCGTTTCCTG GCAGCTACAT TCCTGCTCCT GGCGCTCAGC 60

ACCGCTGCCC AGGCCGAACC GGTGCAGTTC AAGGACTGCG GTTCTGTGGA TGGAGTTATA 120

AAGGAAGTGA ATGTGAGCCC ATGCCCCACC CAACCCTGCC AGCTGAGCAA AGGACAGTCT 180

TACAGCGTCA ATGTCACCTT CACCAGCAAT ATTCAGTCTA AAAGCAGCAA GGCCGTGGTG 240

CATGGCATCC TGATGGGCGT CCCAGTTCCC TTTCCCATTC CTGAGCCTGA TGGTTGTAAG 300

AGTGGAATTA ACTGCCCTAT CCAAAAAGAC AAGACCTATA GCTACCTGAA TAAACTACCA 360

GTGAAAAGCG AATATCCCTC TATAAAACTG GTGGTGGAGT GGCAACTTCA GGATGACAAA 420

AACCAAAGTC TCTTCTGCTG GGAAATCCCA GTACAGATCG TTTCTCATCT CTAAGTGCCT 480

CATTGAGTTC GGTGCATCTG GCCAATGAGT CTGCTGAGAC TCTTGACAGC ACCTCCAGCT 540

CTGCTGCTTC AACAACAGTG ACTTGCTCTC CAATGGTATC CAGTGATTCG TTGAAGAGGA 600

GGTGCTCTGT AGCAGAAACT GAGCTCCGGG TGGCTGGTTC TCAGTGGTTG TCTCATGTCT 660

CTTTTTCTGT CTTAGGTGGT TTCATTAAAT GCAGCACTTG GTTAGCAGAT GTTTAATTTT 720

TTTTTTAACA ACATTAACTT GTGGCCTCTT TCTACACCTG GAAATTTACT CTTGAATAAA 780

TAAAAACTCG TTTGTCTTGT CCAAAAAAAA AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA 840

AAAAAAAAAA AAAAAAAAAA AAA 863

(2) INFORMATION FOR SEQ ID NO:31:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 151 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:31:

Met Arg Phe Leu Ala Ala Thr Phe Leu Leu Leu Ala Leu Ser Thr Ala
1 5 10 15

Ala Gln Ala Glu Pro Val Gln Phe Lys Asp Cys Gly Ser Val Asp Gly
20 25 30

Val Ile Lys Glu Val Asn Val Ser Pro Cys Pro Thr Gln Pro Cys Gln
35 40 45

Leu Ser Lys Gly Gln Ser Tyr Ser Val Asn Val Thr Phe Thr Ser Asn
50 55 60

Ile Gln Ser Lys Ser Ser Lys Ala Val Val His Gly Ile Leu Met Gly
65 70 75 80

Val Pro Val Pro Phe Pro Ile Pro Glu Pro Asp Gly Cys Lys Ser Gly
85 90 95

Ile Asn Cys Pro Ile Gln Lys Asp Lys Thr Tyr Ser Tyr Leu Asn Lys
100 105 110

Leu Pro Val Lys Ser Glu Tyr Pro Ser Ile Lys Leu Val Val Glu Trp
115 120 125

Gln Leu Gln Asp Asp Lys Asn Gln Ser Leu Phe Cys Trp Glu Ile Pro
130 135 140

Val Gln Ile Val Ser His Leu
145 150

(2) INFORMATION FOR SEQ ID NO:32:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1575 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:32:

CATAACAGTC CAGGAAACCA ACAAAAATAA CTCTGAAAGC ATTGAATGCA GCAAAATAAC 60

AATGGATCTC AAGTTCAACA ATTCCAGGAA ATATATTTCT ATCACTGTGC CATCCAAAAC 120

CCAAACAATG TCACCACACA TCAAGTCAGT TGACGACGTT GTGGTACTTG GCATGAATCT 180

CAGCAAGTTT AACAAACTTA CTCAGTTTTT CATATGTGTT GCTGGAGTTT TTGTATTTTA 240

CCTAATTTAT GGGTATTTAC AGGAATTAAT ATTTTCAGTG GAGGGTTTTA AGTCCTGTGG 300

CTGGTACCTT ACCTTAGTGC AGTTTGCCTT TTACTCCATA TTTGGCCTAA TAGAACTTCA 360

GCTTATTCAG GACAAAAGGA GGAGAATACC AGGAAAAACC TACATGATAA TAGCTTTTCT 420

AACTGTGGGT ACTATGGGGT TATCAAACAC TTCCTTGGGC TACCTGAATT ACCCTACCCA 480

AGTCATCTTC AAGTGCTGCA AATTGATTCC TGTTATGCTA GGAGGAGTTT TTATTCAAGG 540

AAAGCGTTAT AATGTTGCAG ATGTGTCTGC TGCCATATGT ATGAGCCTTG GCCTGATATG 600

GTTTACCCTC GCTGACAGCA CAACTGCACC AAATTTCAAC CTGCGGGTAT TGTATTCGTA 660

TTCAATTGGT TTTGTATACA TTTTACTGGG ATTGACATGC ACTAGTGGAT TAGGCCCTGC 720

```
AGTAACATTT TGTGCAAAGA ATCCAGTTCG GACCTATGGT TATGCGTTCC TTTTTTCCCT     780

CACTGGATAT TTTGGAATCT CCTTTGTTCT GGCTTTGATT AAAATTTTTG GTGCACTTAT     840

TGCTGTAACA GTGACAACAG GAAGAAAAGC AATGACCATT GTACTTTCGT TTATATTCTT     900

TGCTAAACCA TTCACGTTTC AGTATGTATG GTCTGGTTTG TTAGTTGTCC TTGGTATATT     960

TCTCAATGTT TACAGCAAAA ATATGGATAA AATAAGACTA CCATCACTGT ATGATTTGAT    1020

AAACAAATCA GTGGAAGCAA GAAAGTCAAG GACGCTGGCA CAGACTGTAT AGACAGTGAT    1080

TGTCCTATTT AAAATAGAAT TTTAAGGGAA CAATCATCAA TTAATTAACT TTCCAAAGGG    1140

ACTGATAAAA ACCAAAGGAT CTGGAGGCAT TGCTATCCCA TTTGTGGACA GATTTCATAT    1200

GAAGTTGTTT TGCGGTGTCA GCCTTTTCTT CAGAGCATTT GTTTGACTGA CTTCCAAAGC    1260

AATCAAGAGA GCCACGTCTA GCAGACTTTA CAATAAAATG TCAATATGAA GGACTGTAAT    1320

TCCTAGCAGT TTATTGAGAA TTTCACTGGA AATGGACCAT GTGTTGCAAG ACTAATTGGC    1380

TATAATTATA TCCTATCAAA GAAATCGATA CGTAATAGCA GATTGTTTTA TATTCATTCC    1440

ATTTTGATGG TGTTATTTAA ATTGATTCTC TGTTATAAGA GTAAACTGAT GAGTTGAAGT    1500

CTGGAGAGAA TAACATTCAT TATAAATAAA ATTATTCTGT GATCTTTTTT CAAAAAAAAA    1560

AAAAAAAAAA AAAAA                                                     1575
```

(2) INFORMATION FOR SEQ ID NO:33:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 336 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:33:

```
Met Asp Leu Lys Phe Asn Asn Ser Arg Lys Tyr Ile Ser Ile Thr Val
1               5                  10                  15

Pro Ser Lys Thr Gln Thr Met Ser Pro His Ile Lys Ser Val Asp Asp
            20                  25                  30

Val Val Val Leu Gly Met Asn Leu Ser Lys Phe Asn Lys Leu Thr Gln
        35                  40                  45

Phe Phe Ile Cys Val Ala Gly Val Phe Val Phe Tyr Leu Ile Tyr Gly
    50                  55                  60

Tyr Leu Gln Glu Leu Ile Phe Ser Val Glu Gly Phe Lys Ser Cys Gly
65                  70                  75                  80

Trp Tyr Leu Thr Leu Val Gln Phe Ala Phe Tyr Ser Ile Phe Gly Leu
                85                  90                  95
```

Ile Glu Leu Gln Leu Ile Gln Asp Lys Arg Arg Arg Ile Pro Gly Lys
100 105 110

Thr Tyr Met Ile Ile Ala Phe Leu Thr Val Gly Thr Met Gly Leu Ser
115 120 125

Asn Thr Ser Leu Gly Tyr Leu Asn Tyr Pro Thr Gln Val Ile Phe Lys
130 135 140

Cys Cys Lys Leu Ile Pro Val Met Leu Gly Gly Val Phe Ile Gln Gly
145 150 155 160

Lys Arg Tyr Asn Val Ala Asp Val Ser Ala Ala Ile Cys Met Ser Leu
165 170 175

Gly Leu Ile Trp Phe Thr Leu Ala Asp Ser Thr Thr Ala Pro Asn Phe
180 185 190

Asn Leu Arg Val Leu Tyr Ser Tyr Ser Ile Gly Phe Val Tyr Ile Leu
195 200 205

Leu Gly Leu Thr Cys Thr Ser Gly Leu Gly Pro Ala Val Thr Phe Cys
210 215 220

Ala Lys Asn Pro Val Arg Thr Tyr Gly Tyr Ala Phe Leu Phe Ser Leu
225 230 235 240

Thr Gly Tyr Phe Gly Ile Ser Phe Val Leu Ala Leu Ile Lys Ile Phe
245 250 255

Gly Ala Leu Ile Ala Val Thr Val Thr Thr Gly Arg Lys Ala Met Thr
260 265 270

Ile Val Leu Ser Phe Ile Phe Phe Ala Lys Pro Phe Thr Phe Gln Tyr
275 280 285

Val Trp Ser Gly Leu Leu Val Val Leu Gly Ile Phe Leu Asn Val Tyr
290 295 300

Ser Lys Asn Met Asp Lys Ile Arg Leu Pro Ser Leu Tyr Asp Leu Ile
305 310 315 320

Asn Lys Ser Val Glu Ala Arg Lys Ser Arg Thr Leu Ala Gln Thr Val
325 330 335

(2) INFORMATION FOR SEQ ID NO:34:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1078 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:34:

CTTCATCACA GGATCAACAC ATTTCATCTG GGCTTCTTAA ATCTAAATCT TTAAAATGAC 60

```
TAAGTTTTCT TCCTTTTCTC TGTTTTTCCT AATAGTTGGG GCTTATATGA CTCATGTGTG      120

TTTCAATATG GAAATTATTG GAGGGAAAGA AGTGTCACCT CATTCCAGGC CATTTATGGC      180

CTCCATCCAG TATGGCGGAC ATCACGTTTG TGGAGGTGTT CTGATTGATC CACAGTGGGT      240

GCTGACAGCA GCCCACTGCC AATATCGGTT TACCAAAGGC CAGTCTCCCA CTGTGGTTTT      300

AGGCGCACAC TCTCTCTCAA AGAATGAGGC CTCCAAACAA ACACTGGAGA TCAAAAAATT      360

TATACCATTC TCAAGAGTTA CATCAGATCC TCAATCAAAT GATATCATGC TGGTTAAGCT      420

TCAAACAGCC GCAAAACTCA ATAAACATGT CAAGATGCTC CACATAAGAT CCAAAACCTC      480

TCTTAGATCT GGAACCAAAT GCAAGGTTAC TGGCTGGGGA GCCACCGATC CAGATTCATT      540

AAGACCTTCT GACACCCTGC GAGAAGTCAC TGTTACTGTC CTAAGTCGAA AACTTTGCAA      600

CAGCCAAAGT TACTACAACG GCGACCCTTT TATCACCAAA GACATGGTCT GTGCAGGAGA      660

TGCCAAAGGC CAGAAGGATT CCTGTAAGGG TGACTCAGGG GGCCCCTTGA TCTGTAAAGG      720

TGTCTTCCAC GCTATAGTCT CTGGAGGTCA TGAATGTGGT GTTGCCACAA AGCCTGGAAT      780

CTACACCCTG TTAACCAAGA AATACCAGAC TTGGATCAAA AGCAACCTTG TTCCGCCTCA      840

TACAAATTAA GTTACAAATA ATTTTATTGG ATGCACTTGC TTCTTTTTTC CTAATATGCT      900

CGCAGGTTAG AGTTGGGTGT AAGTAAAGCA GAGCACATAT GGGGTCCATT TTTGCACTTG      960

TAAGTCATTT TATTAAGGAA TCAAGTTCTT TTTCACTTGT ATCACTGATG TATTTCTACC     1020

ATGCTGGTTT TATTCTAAAT AAAATTTAGA AGACTCTCAA AAAAAAAAAA AAAAAAAA       1078
```

(2) INFORMATION FOR SEQ ID NO:35:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 264 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:35:

```
Met Thr Lys Phe Ser Ser Phe Ser Leu Phe Phe Leu Ile Val Gly Ala
1               5                  10                  15

Tyr Met Thr His Val Cys Phe Asn Met Glu Ile Ile Gly Gly Lys Glu
            20                  25                  30

Val Ser Pro His Ser Arg Pro Phe Met Ala Ser Ile Gln Tyr Gly Gly
        35                  40                  45

His His Val Cys Gly Gly Val Leu Ile Asp Pro Gln Trp Val Leu Thr
    50                  55                  60

Ala Ala His Cys Gln Tyr Arg Phe Thr Lys Gly Gln Ser Pro Thr Val
```

65 70 75 80

Val Leu Gly Ala His Ser Leu Ser Lys Asn Glu Ala Ser Lys Gln Thr
85 90 95

Leu Glu Ile Lys Lys Phe Ile Pro Phe Ser Arg Val Thr Ser Asp Pro
100 105 110

Gln Ser Asn Asp Ile Met Leu Val Lys Leu Gln Thr Ala Ala Lys Leu
115 120 125

Asn Lys His Val Lys Met Leu His Ile Arg Ser Lys Thr Ser Leu Arg
130 135 140

Ser Gly Thr Lys Cys Lys Val Thr Gly Trp Gly Ala Thr Asp Pro Asp
145 150 155 160

Ser Leu Arg Pro Ser Asp Thr Leu Arg Glu Val Thr Val Thr Val Leu
165 170 175

Ser Arg Lys Leu Cys Asn Ser Gln Ser Tyr Tyr Asn Gly Asp Pro Phe
180 185 190

Ile Thr Lys Asp Met Val Cys Ala Gly Asp Ala Lys Gly Gln Lys Asp
195 200 205

Ser Cys Lys Gly Asp Ser Gly Gly Pro Leu Ile Cys Lys Gly Val Phe
210 215 220

His Ala Ile Val Ser Gly Gly His Glu Cys Gly Val Ala Thr Lys Pro
225 230 235 240

Gly Ile Tyr Thr Leu Leu Thr Lys Lys Tyr Gln Thr Trp Ile Lys Ser
245 250 255

Asn Leu Val Pro Pro His Thr Asn
260

(2) INFORMATION FOR SEQ ID NO:36:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1686 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:36:

CGATAATCTT CTTCCATTTT TGCGGAAATT TATTGCATCC TTCTTTAAAC CGGGGTTTGA 60

GAAGTATAAT AACTTGGATC TGTTTCGGTA TCTCTTAAAT ATTCCAGGAC CAATTGACAT 120

TCCATCTCGT TTATGTAAAG GGAATTTTGA TGATGATATG TTTAACCACC AAGTTCCTTA 180

TTTGTGGCTG ATTTACTGCC TTTGTCATCC TCTTCAATCA AGTATTAAAG AAACAGTGGA 240

GGCATATGAG GCAGCATTAG GGGTGGCTAT GAGATGTGAT ATAGTACAGA AGATATGGAT 300

GGATTATCTT GTCTTTGCAA ATAATAGAGC TGCTGGATCC AGAAACAAAG TTCAAGAATT 360

CAAATTTTTT ACTGATTTAG TGAATAGATG TTTGGTTACA GTCCCTGCCC GATACCCCAT 420

TCCTTTTAGC AGTGCTGATT ACTGGTCCAA CTATGAATTT CATAATAGGG TTATTTTCTT 480

TTATTTGAGC TGTGTTCCAA AGACCCAGCA TTCCAAAACC TTGGAACGGT TTTGTTCAGT 540

TATGCCAGCT AATTCTGGAC TTGCATTGAG GTTACTTCAA CATGAATGGG AAGAAAGCAA 600

TGTTCAGATT CTGAAACTTC AAGCCAAGAT GTTTACATAT AATATCCCAA CATGCCTGGC 660

CACCTGGAAA ATAGCCATTG CTGCTGAGAT TGTTCTAAAG GGACAAAGAG AGGTCCACCG 720

TTTATATCAG AGAGCCTTAC AGAAGTTACC TCTTTGTGCA TCACTGTGGA AAGATCAACT 780

CTTGTTTGAA GCATCAGAAG GAGGTAAAAC TGATAACCTG AGAAAACTAG TTTCCAAGTG 840

CCAAGAGATT GGAGTCAGCC TAAATGAGCT CTTAAATTTA AACAGTAACA AAACAGAAAG 900

CAAGAATCAC TGAACACTGG GTGCAGTCAG TTCTAAGTCC TTATAATAAT TGCCAAAATT 960

ATTTGAATGA TTCTTCAAGA TTAGGCTGAT CCCTGGCTAA GGTCTGTGTA AGGCAGACAA 1020

GCGTTATTGA TCATATCAAG TTCCCTACAA TATCCTGTCC TCAAAACCGG AAGCAATGAA 1080

CATGATCCTC TTCGGTTGGA TAAATGAACT TCCTGTTTGG CCTGCTTCTA GGCCCTGCCA 1140

GATTCTCATA ACATCATATA CGTAAGTATA GTTCCTCAAA GTGACTGACA TTTATTTTAA 1200

TTTTGCTTTG TTTTTTTTTA TTTTCTCCCC CATTCCTTTA TTTTGTGTTA TTCCTGACTC 1260

ACTTGACACT CTCTGATGCC TGAGAGATTC CTGTTTGGGA TTTAATATCC AGGGCTGTGT 1320

TTACAGTAAA AAAAGCAGGC AGTCCCTTTT AGTTTTTCCT TTTTAAATTT TTTTGAGATT 1380

CTTCATTTCA GGATTTTAAA ACTATAGCAG TCCATCTTAA GGAAAGTGTA ACTGCCATGG 1440

CCACAAGTCT GCTAGTTGCA CTTGAATGCT CTATCAGGGT TGTTTATTAC CCTTTCTACG 1500

TTCTGGACTC CTTGCCGAGA CTGTTTAACT TGAAGATTAA AGAAACTATT GCAAATGCCA 1560

GTGCATCAGA ACCTAAGAGT GGTCAAATAT TATGTGCAAT TTTTTTGTAA AGAAATTTTA 1620

ATTTATAATA AAGTTTAACA GTTTAAAGAA CAAAAAAAAA AAAAAAAAAA AAAAAAAAAA 1680

AAAAAA 1686

(2) INFORMATION FOR SEQ ID NO:37:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 251 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:37:

```
Met Phe Asn His Gln Val Pro Tyr Leu Trp Leu Ile Tyr Cys Leu Cys
1               5                  10                  15

His Pro Leu Gln Ser Ser Ile Lys Glu Thr Val Glu Ala Tyr Glu Ala
            20                  25                  30

Ala Leu Gly Val Ala Met Arg Cys Asp Ile Val Gln Lys Ile Trp Met
        35                  40                  45

Asp Tyr Leu Val Phe Ala Asn Asn Arg Ala Ala Gly Ser Arg Asn Lys
    50                  55                  60

Val Gln Glu Phe Lys Phe Phe Thr Asp Leu Val Asn Arg Cys Leu Val
65                  70                  75                  80

Thr Val Pro Ala Arg Tyr Pro Ile Pro Phe Ser Ser Ala Asp Tyr Trp
                85                  90                  95

Ser Asn Tyr Glu Phe His Asn Arg Val Ile Phe Phe Tyr Leu Ser Cys
            100                 105                 110

Val Pro Lys Thr Gln His Ser Lys Thr Leu Glu Arg Phe Cys Ser Val
        115                 120                 125

Met Pro Ala Asn Ser Gly Leu Ala Leu Arg Leu Leu Gln His Glu Trp
    130                 135                 140

Glu Glu Ser Asn Val Gln Ile Leu Lys Leu Gln Ala Lys Met Phe Thr
145                 150                 155                 160

Tyr Asn Ile Pro Thr Cys Leu Ala Thr Trp Lys Ile Ala Ile Ala Ala
                165                 170                 175

Glu Ile Val Leu Lys Gly Gln Arg Glu Val His Arg Leu Tyr Gln Arg
            180                 185                 190

Ala Leu Gln Lys Leu Pro Leu Cys Ala Ser Leu Trp Lys Asp Gln Leu
        195                 200                 205

Leu Phe Glu Ala Ser Glu Gly Gly Lys Thr Asp Asn Leu Arg Lys Leu
    210                 215                 220

Val Ser Lys Cys Gln Glu Ile Gly Val Ser Leu Asn Glu Leu Leu Asn
225                 230                 235                 240

Leu Asn Ser Asn Lys Thr Glu Ser Lys Asn His
                245                 250
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What is claimed is:

1. A composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:2;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:2 from nucleotide 1 to nucleotide 1014;

(c) a polynucleotide comprising the nucleotide sequence of the full length protein coding sequence of clone G52_24 deposited under accession number ATCC 98028;

(d) a polynucleotide encoding the full length protein encoded by the cDNA insert of clone G52_24 deposited under accession number ATCC 98028;

(e) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone G52_24 deposited under accession number ATCC 98028;

(f) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone G52_24 deposited under accession number ATCC 98028;

(g) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:3;

(h) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:3 having biological activity;

(i) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:26 from nucleotide 732 to nucleotide 1274;

(j) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:27;

(k) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(d) or (i) above;

(l) a polynucleotide which encodes a species homologue of the protein of (g), (h) or (j) above; and

(m) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(i).

2. A composition of claim 1 wherein said polynucleotide is operably linked to an expression control sequence.

3. A host cell transformed with a composition of claim 2.

4. The host cell of claim 3, wherein said cell is a mammalian cell.

5. A process for producing a protein, which comprises:

(a) growing a culture of the host cell of claim 3 in a suitable culture medium; and

(b) purifying the protein from the culture

6. A protein produced according to the process of claim 5.

7. The protein of claim 6 comprising a mature protein.

8. A composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:3;

(b) the amino acid sequence of SEQ ID NO:3 from amino acid 201 to amino acid 221;

(c) fragments of the amino acid sequence of SEQ ID NO:3; and

(d) the amino acid sequence encoded by the cDNA insert of clone G52_24 deposited under accession number ATCC98028;

(e) the amino acid sequence of SEQ ID NO:27;

(f) the amino acid sequence of SEQ ID NO:27 beginning with amino acid 41;

the protein being substantially free from other mammalian proteins.

9. The composition of claim 8, wherein said protein comprises the amino acid sequence of SEQ ID NO:3.

10. The composition of claim 8, wherein said protein comprises the amino acid sequence of SEQ ID NO:2 from amino acid 201 to amino acid 221.

11. The composition of claim 8, further comprising a pharmaceutically acceptable carrier.

12. A method for preventing, treating or ameliorating a medical condition which comprises administering to a mammalian subject a therapeutically effective amount of a composition of claim 11.

13. The gene corresponding to the cDNA sequence of SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:4 or SEQ ID NO:26.

14. A composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:5;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:5 from nucleotide 181 to nucleotide 325;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:5 from nucleotide 274 to nucleotide 325;

(d) a polynucleotide comprising the nucleotide sequence of the full length protein coding sequence of clone M97_2 deposited under accession number ATCC 98028;

(e) a polynucleotide encoding the full length protein encoded by the cDNA insert of clone M97_2 deposited under accession number ATCC 98028;

(f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone M97_2 deposited under accession number ATCC 98028;

(g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone M97_2 deposited under accession number ATCC 98028;

(h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:6;

(i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:6 having biological activity;

(j) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:28 from nucleotide 171 to nucleotide 587;

(k) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:29;

(l) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) or (j) above; and

(m) a polynucleotide which encodes a species homologue of the protein of (h), (i) or (k) above.

15. A composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:6;

(b) the amino acid sequence of SEQ ID NO:6 from amino acid 1 to amino acid 48;

(c) fragments of the amino acid sequence of SEQ ID NO:6; and

(d) the amino acid sequence encoded by the cDNA insert of clone M97_2 deposited under accession number ATCC98028;

(e) the amino acid sequence of SEQ ID NO:29;

the protein being substantially free from other mammalian proteins.

16. The gene corresponding to the cDNA sequence of SEQ ID NO:5, SEQ ID NO:7 or SEQ ID NO:28.

17. A composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:8;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:8 from nucleotide 36 to nucleotide 522;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:8 from nucleotide 93 to nucleotide 522;

(d) a polynucleotide comprising the nucleotide sequence of the full length protein coding sequence of clone H1075_1 deposited under accession number ATCC 98028;

(e) a polynucleotide encoding the full length protein encoded by the cDNA insert of clone H1075_1 deposited under accession number ATCC 98028;

(f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone H1075_1 deposited under accession number ATCC 98028;

(g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone H1075_1 deposited under accession number ATCC 98028;

(h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:9;

(i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:9 having biological activity;

(j) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:30 from nucleotide 19 to nucleotide 471;

(k) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:31;

(l) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) or (j) above; and

(m) a polynucleotide which encodes a species homologue of the protein of (h), (i) or (k) above .

18. A composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:9;

(b) the amino acid sequence of SEQ iD NO:9 from amino acid 1 to amino acid 101;

(c) fragments of the amino acid sequence of SEQ ID NO:9;

(d) the amino acid sequence encoded by the cDNA insert of clone H1075_1 deposited under accession number ATCC98028;

(e) the amino acid sequence of SEQ ID NO:31; and

(f) the amino acid sequence of SEQ ID NO:31 beginning with amino acid 20;

the protein being substantially free from other mammalian proteins.

19. The gene corresponding to the cDNA sequence of SEQ ID NO:8, SEQ ID NO:10 or SEQ ID NO:30.

20. A composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:11;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:11 from nucleotide 88 to nucleotide 499;

(c) a polynucleotide comprising the nucleotide sequence of the full length protein coding sequence of clone J59_41 deposited under accession number ATCC 98028;

(d) a polynucleotide encoding the full length protein encoded by the cDNA insert of clone J59_41 deposited under accession number ATCC 98028;

(e) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone J59_41 deposited under accession number ATCC 98028;

(f) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone J59_41 deposited under accession number ATCC 98028;

(g) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:12;

(h) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:12 having biological activity;

(i) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:32 from nucleotide 62 to nucleotide 1069;

(j) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:33 beginning with amino acid 185;

(k) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(f) or (i) above;

(l) a polynucleotide which encodes a species homologue of the protein of (g), (h) or (j) above; and

(m) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(i).

21. A composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:12;

(b) the amino acid sequence of SEQ ID NO:12 from amino acid 45 to amino acid 113;

(c) fragments of the amino acid sequence of SEQ ID NO:12;

(d) the amino acid sequence encoded by the cDNA insert of clone J59_41 deposited under accession number ATCC98028;

(e) the amino acid sequence of SEQ ID NO:33;

(f) the amino acid sequence of SEQ ID NO:33 beginning with amino acid 185;

the protein being substantially free from other mammalian proteins.

22. The gene corresponding to the cDNA sequence of SEQ ID NO:11 or SEQ ID NO:13 or SEQ ID NO:33.

23. A composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:14;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:14 from nucleotide 138 to nucleotide 479;

(c) a polynucleotide comprising the nucleotide sequence of the full length protein coding sequence of clone H83_22 deposited under accession number ATCC 98028;

(d) a polynucleotide encoding the full length protein encoded by the cDNA insert of clone H83_22 deposited under accession number ATCC 98028;

(e) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone H83_22 deposited under accession number ATCC 98028;

(f) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone H83_22 deposited under accession number ATCC 98028;

(g) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:15;

(h) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:15 having biological activity;

(i) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:34 from nucleotide 56 to nucleotide 847;

(j) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:35;

(k) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(f) or (i) above;

(l) a polynucleotide which encodes a species homologue of the protein of (g), (h) or (j) above ; and

(m) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(j).

24. A composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:15;

(b) fragments of the amino acid sequence of SEQ ID NO:15;

(c) the amino acid sequence encoded by the cDNA insert of clone H83_22 deposited under accession number ATCC98028; and

(d) the amino acid sequence of SEQ ID NO:35;

the protein being substantially free from other mammalian proteins.

25. The gene corresponding to the cDNA sequence of SEQ ID NO:14 or SEQ ID NO:16 or SEQ ID NO:34.

26. A composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:17;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:17 from nucleotide 149 to nucleotide 461;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:17 from nucleotide 212 to nucleotide 461;

(d) a polynucleotide comprising the nucleotide sequence of the full length protein coding sequence of clone J143_1 deposited under accession number ATCC 98028;

(e) a polynucleotide encoding the full length protein encoded by the cDNA insert of clone J143_1 deposited under accession number ATCC 98028;

(f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone J143_1 deposited under accession number ATCC 98028;

(g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone J143_1 deposited under accession number ATCC 98028;

(h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:18;

(i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:18 having biological activity;

(j) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:36 from nucleotide 158 to nucleotide 910;

(k) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:37;

(l) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) or (j) above; and

(m) a polynucleotide which encodes a species homologue of the protein of (h), (i) or (k) above.

27. A composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:18;

(b) fragments of the amino acid sequence of SEQ ID NO:18;

(c) the amino acid sequence encoded by the cDNA insert of clone J143_1 deposited under accession number ATCC98028;

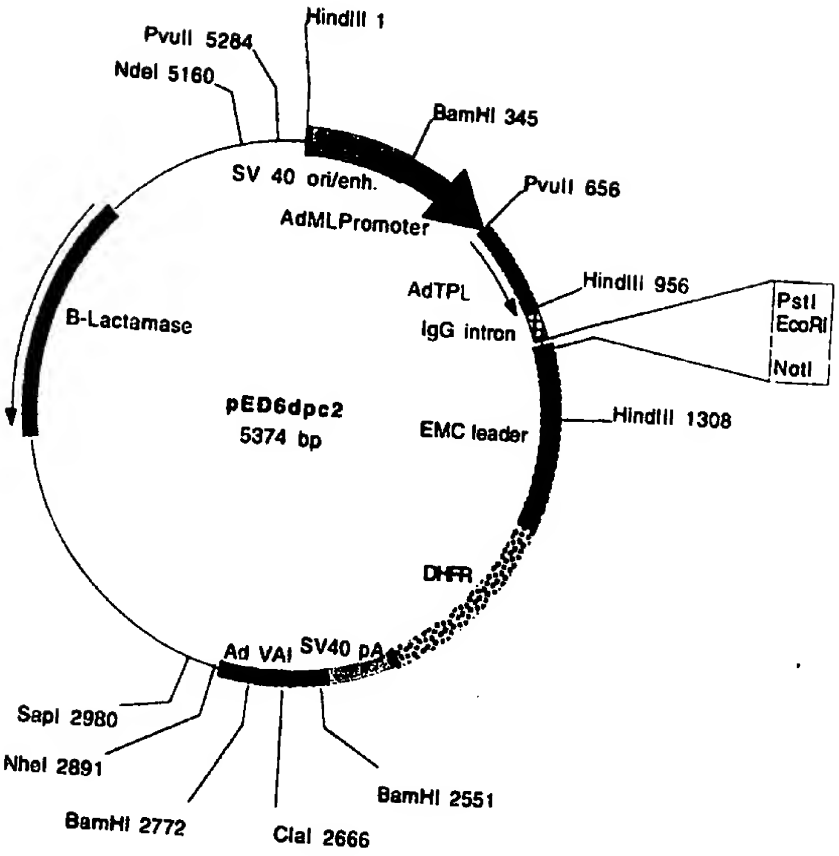
(d) the amino acid sequence of SEQ ID NO:36; and

(e) the amino acid sequence of SEQ ID NO:36 beginning with amino acid 22;

the protein being substantially free from other mammalian proteins.

28. The gene corresponding to the cDNA sequence of SEQ ID NO:17 or SEQ ID NO:19 or SEQ ID NO:36.

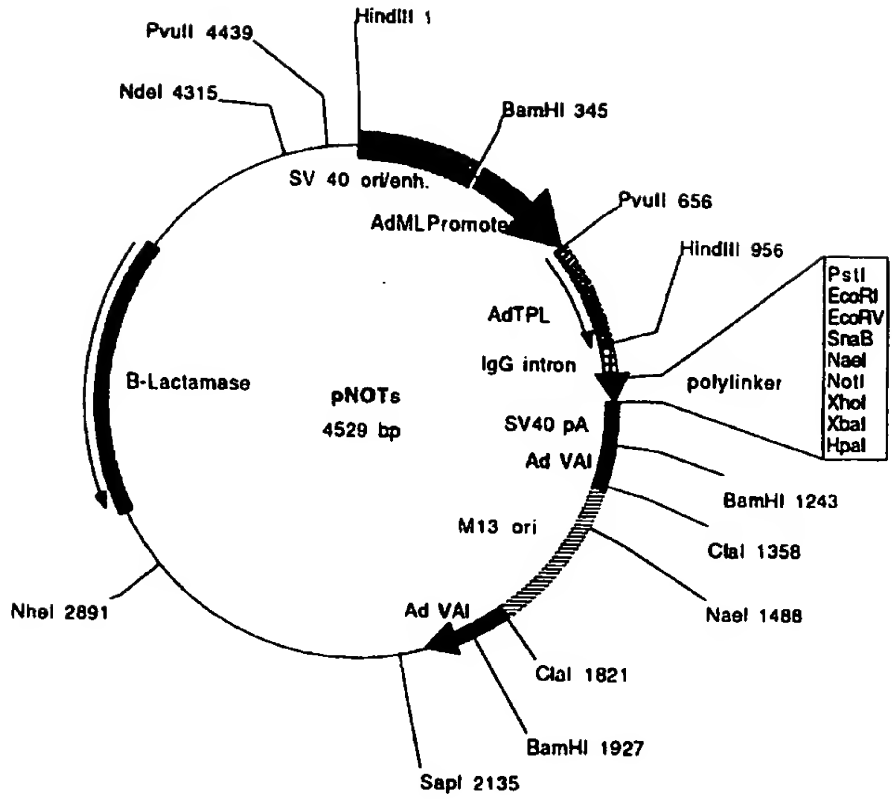
FIGURE 1A



Plasmid name: pED6dpc2
Plasmid size: 5374 bp

Comments/References: pED6dpc2 is derived from pED6dpc1 by insertion of a new polylinker to facilitate cDNA cloning. SST cDNAs are cloned between EcoRI and NotI. pED vectors are described in Kaufman et al.(1991), NAR 19: 4485-4490.

FIGURE 1B



Plasmid name: pNOTs
Plasmid size: 4529 bp

Comments/References: pNOTs is a derivative of pMT2 (Kaufman et al,1989. Mol.Cell.Biol.9:1741-1750). DHFR was deleted and a new polylinker was inserted between EcoRI and HpaI. M13 origin of replication was inserted in the ClaI site. SST cDNAs are cloned between EcoRI and NotI